Journal of
THE CHEMICAL SOCIETY

Committee of Publication

Chairman: Sir Cyril Hinshelwood, M.A., Sc.D., F.R.S.

Sir Wallace Akers, C.B.E., D.C.L., D.Sc., F.R.S.
J. S. Anderson, M.Sc., Ph.D., F.R.S.
D. H. R. Barton, Ph.D., D.Sc., F.R.I.C.
C. E. H. Bawn, B.Sc., Ph.D., F.R.S.
D. J. Bell, Sc.D., Ph.D.
R. P. Bell, M.A., B.Sc., F.R.S.
E. J. Bowen, M.A., D.Sc., F.R.S.
H. Burton, Ph.D., D.Sc., F.R.I.C.
A. H. Cook, D.Sc., F.R.I.C., F.R.S.
C. A. Coulson, M.A., D.Sc., F.R.S.
F. S. Dainton, M.A., Ph.D.
C. W. Davies, D.Sc., F.R.I.C.
H. J. Emeléus, D.Sc., A.R.C.S., F.R.S.
F. Fairbrother, D.Sc.
R. D. Haworth, D.Sc., Ph.D., F.R.S.
E. D. Hughes, D.Sc., F.R.I.C., F.R.S.
H. R. Ing, M.A., D.Phil., F.R.S.
C. K. Ingold, D.Sc., F.R.I.C., F.R.S.
H. M. N. H. Irving, M.A., D.Phil., F.R.I.C.
F. G. Mann, Sc.D., F.R.I.C., F.R.S.
R. A. Morton, D.Sc., Ph.D., F.R.S.
L. N. Owen, Ph.D., D.Sc., F.R.I.C.
J. M. Robertson, M.A., D.Sc., F.R.S.
H. N. Rydon, D.Sc., D.Phil., F.R.I.C.
N. Sheppard, M.A., Ph.D.
C. W. Shoppee, D.Sc., D.Phil., F.R.I.C.
W. F. Short, D.Sc., M.Sc.
R. Spence, C.B., Ph.D., D.Sc., F.R.I.C.
M. Stacey, Ph.D., D.Sc., F.R.S.
L. E. Sutton, M.A., D.Phil., F.R.S.
J. Walker, Ph.D., D.Phil., D.Sc.
W. A. Waters, M.A., Sc.D., F.R.I.C.
T. S. Wheeler, Ph.D., D.Sc., F.R.I.C.

Editor

R. S. Cahn, M.A., D.Phil.Nat., F.R.I.C.

Assistant Editors

A. D. Mitchell, D.Sc., F.R.I.C.
L. C. Cross, Ph.D., A.R.C.S., F.R.I.C.
A. E. Somerfield, B.A., B.Sc.

MARCH, 1954

Subscription rate to non-Fellows £10 0s. 0d. per annum post free

LONDON: THE CHEMICAL SOCIETY, BURLINGTON HOUSE, W.1.

THE CHEMICAL SOCIETY

PATRON

HER MAJESTY THE QUEEN

President

C. K. Ingold, D.Sc., F.R.I.C., F.R.S.

Vice-Presidents

who have filled the office of President

F. G. Donnan, C.B.E., D.Sc., LL.D., F.R.S.
Sir Ian Heilbron, D.S.O., D.Sc., LL.D., F.R.S.
Sir Cyril Hinshelwood, M.A., Sc.D., F.R.S.
W. H. Mills, M.A., Sc.D., F.R.S.
Sir Eric Rideal, M.B.E., M.A., D.Sc., F.R.S.
Sir Robert Robinson, O.M., D.Sc., LL.D., F.R.S.

Vice-Presidents

G. R. Clemo, D.Phil., D.Sc., F.R.S.
R. D. Haworth, D.Sc., Ph.D., F.R.S.
D. H. Hey, Ph.D., D.Sc., F.R.I.C.
E. L. Hirst, D.Sc., LL.D., F.R.S.
Sir John Simonsen, D.Sc., F.R.I.C., F.R.S.
M. Stacey, Ph.D., D.Sc., F.R.S.

Treasurer

Sir Wallace Akers, C.B.E., D.C.L., D.Sc., F.R.S.

Secretaries

H. Burton, Ph.D., D.Sc., F.R.I.C.
E. D. Hughes, D.Sc., F.R.I.C., F.R.S.
L. E. Sutton, M.A., D.Phil., F.R.S.

Ordinary Members of Council

G. Baddeley, M.Sc., Ph.D., D.Sc.
Wilson Baker, M.A., D.Sc., F.R.S.
D. H. R. Barton, Ph.D., D.Sc., F.R.I.C.
J. Bell, D.Sc., Ph.D., F.R.I.C.
R. P. Bell, M.A., B.Sc., F.R.S.
F. Bergel, D.Phil.Nat., D.Sc., F.R.I.C.
Neil Campbell, D.Sc., Ph.D.
J. Chatt, M.A., Ph.D., F.R.I.C.
M. J. S. Dewar, M.A., D.Phil.
I. J. Faulkner, B.Sc., Ph.D., F.R.I.C.
S. J. Gregg, Ph.D., A.R.C.S., F.R.I.C.
Brynmor Jones, Sc.D., Ph.D., F.R.I.C.
F. B. Kipping, M.A., Ph.D.
E. A. Moelwyn-Hughes, D.Phil., D.Sc., Sc.D.
M. W. Perrin, C.B.E., M.A., F.R.I.C.
H. M. Powell, M.A., B.Sc., F.R.S.
A. Robertson, M.A., Ph.D., F.R.S.
M. A. T. Rogers, B.Sc., Ph.D., A.R.I.C.
C. W. Shoppee, D.Sc., D.Phil., F.R.I.C.
J. W. Smith, Ph.D., D.Sc., F.R.I.C.
T. S. Stevens, B.Sc., D.Phil., A.R.I.C.
A. R. J. P. Ubbelohde, M.A., D.Sc., F.R.S.
A. I. Vogel, D.Sc., D.I.C., F.R.I.C.

Ex-Officio Member of Council

W. Wardlaw, C.B.E., D.Sc., F.R.I.C. (*Chairman of the Joint Library Committee*)

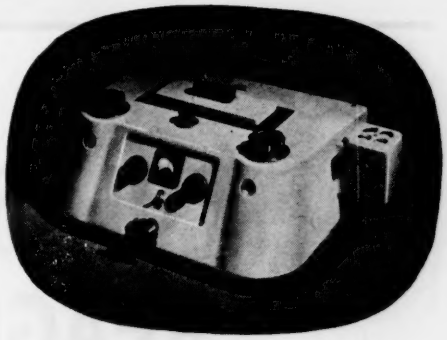
General Secretary

J. R. Ruck Keene, M.B.E., T.D., B.A.

Librarian

A. E. Cummins

Telephone Numbers: Regent 0675/6



THE Unicam SP.600 Spectrophotometer for the visible region represents a nice combination of optical and electronic design. A simple Littrow monochromator of high resolving power with a glass prism is used to give continuous wavelength selection between 3,600Å and 10,000Å in a precise and convenient manner. The vacuum photocell and amplifier have a sensitivity that allows the use of narrow slit widths with a corresponding freedom from spectral impurity. The null-point measuring system eliminates internal circuit effects and does not assume linearity of the amplifier. Alternative battery or mains operation can be provided.

The SP.600 is highly sensitive and suitable for solutions of low optical density as it will measure accurately small differences in concentration. Operation is simple and rapid, up to four samples being examined together, and readings are taken as either optical density or percentage transmission. A series of routine checks at one closely defined wavelength can be made with the same ease as a complete absorption spectrum over the wavelength range available. The spectrophotometer is strongly built, requires little maintenance and is moderately priced.

Please write for the new descriptive leaflet which describes the instrument in detail.

UNICAM
SPECTROPHOTOMETERS

UNICAM INSTRUMENTS LTD · ARBURY WORKS · CAMBRIDGE

U133B

POLARITAN REAGENTS

for polarographic analysis

Since the original introduction by Hopkin & Williams of POLARITAN REAGENTS in 1951, the list of reagents has been added to from time to time and the full range of reagents now available is given below :—

AMMONIA SOLUTION S.G. 0.88	POTASSIUM HYDROXIDE
AMMONIUM CHLORIDE	POTASSIUM THIOCYANATE
BARIUM CHLORIDE	SULPHURIC ACID
CITRIC ACID	TARTARIC ACID
HYDROCHLORIC ACID	GELATINE
NITRIC ACID	LITHIUM HYDROXIDE
POTASSIUM CHLORIDE	SODIUM SULPHITE

POLARITAN REAGENTS are supplied only by Hopkin & Williams, Ltd., and the standards and methods of test have been formulated in collaboration with

Tinsley (Industrial Instruments), Ltd.

A copy of the booklet "POLARITAN Standards for Polarographic Reagents" will be sent free, on request.

HOPKIN & WILLIAMS LTD

Manufacturers of pure chemicals for Research and Analysis

FRESHWATER ROAD · CHADWELL HEATH · ESSEX

Whiffens announce

BIG REDUCTION IN PRICE OF HYDRAZINE SULPHATE

DELIVERY EX STOCK
Write or telephone for information and prices to...

WHIFFENS

fine chemicals for industry

WHIFFEN & SONS LTD · NORTH WEST HOUSE · MARYLEBONE RD · LONDON N.W.1
Telephone: Paddington 1041/6 Telegrams: Whiffen, Norwest, London

LIGHT'S 1954 catalogue

is now being distributed

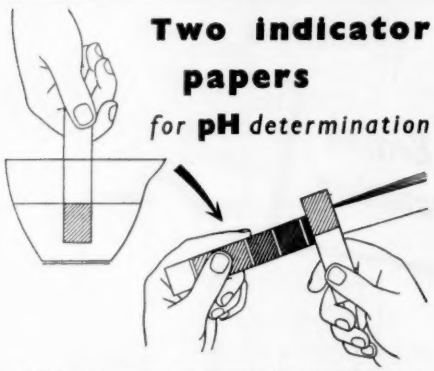
please let us know if you have not received your copy

amino acids, peptides, enzymes, biochemicals, reagents, vitamins, hydrides, pyrimidines, sugars, synthetic drugs, intermediates, solvents, etc.

L. LIGHT & Co. Ltd · Colnbrook · Bucks

Sodium tetraphenylboron—new reagent for Potassium, ammonium and some organic nitrogen compounds—write for *review* to

L. LIGHT & Co. Ltd · Colnbrook · Bucks



Two indicator papers

for **pH** *determination*

UNIVERSAL One paper covering completely the range from 1 to 10 enabling pH values to be checked to within 0.5 pH.

COMPARATOR Four separate books for work requiring greater accuracy. With these papers the pH value of any solution can be ascertained to within 0.3 pH.

Descriptive leaflet will be sent free on request.

JOHNSONS OF HENDON LTD

London, N.W.4
Est. 1743

SILICATES OF ALUMINIUM CALCIUM MAGNESIUM

for Pharmaceutical and Industrial use

Samples and quotations from

KAYLENE TERRA SIC TILLATA BRAND

KAYLENE (CHEMICALS) LTD.
WATERLOO ROAD, LONDON, N.W.2

H. K. LEWIS BOOKS ON THE CHEMICAL AND ALLIED SCIENCES

Scientific and Technical Books. :: Large Stock of Recent Editions. :: Foreign Books not in Stock obtained under Special Licence. :: Catalogues on request.

LENDING LIBRARY—Scientific and Technical

ANNUAL SUBSCRIPTION FROM 25s. *PROSPECTUS FREE ON APPLICATION*

THE LIBRARY CATALOGUE containing classified Index of Authors and Subjects revised to December 1949. Pp. xii + 1152. To subscribers 17s. 6d. net. To non-subscribers 35s. net., postage 1s. 3d. Supplement 1950 to 1952. To subscribers 3s. net; to non-subscribers 6s. net; postage 6d.

BI-MONTHLY LIST OF NEW BOOKS AND NEW EDITIONS ADDED TO THE LIBRARY POST FREE TO SUBSCRIBERS REGULARLY

H. K. LEWIS & Co. Ltd., 136 Gower Street, London, W.C.1

Telephone: EUSton 4282 (7 lines)

Annual Reports on the Progress of Chemistry for 1953

VOLUME L

Publishing July 1954

Copies of this regular publication of the Chemical Society may now be ordered.

Price:

Thirty shillings, post free

THE CHEMICAL SOCIETY

Burlington House · London, W.1

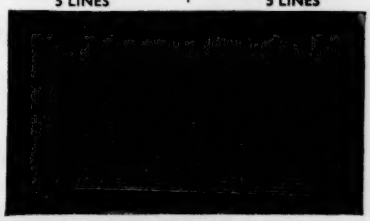
CHEMICAL ENGINEERS and CONSULTING CONTRACTORS

PRODORITE LTD.

EST. 26 YEARS

Head Off: EAGLE WORKS WEDNESBURY STAFFS. Telephone: WED 0284 5 LINES

London Off: ARTILLERY HO. ARTILLERY ROW LONDON, S.W.1 Telephone: ABBEY 3816 5 LINES



THE WORLD'S GREATEST BOOKSHOP

FOYLES FOR BOOKS

New, secondhand and rare Books on every subject. Stock of over three million volumes. Subscriptions taken for British, American and Continental magazines.

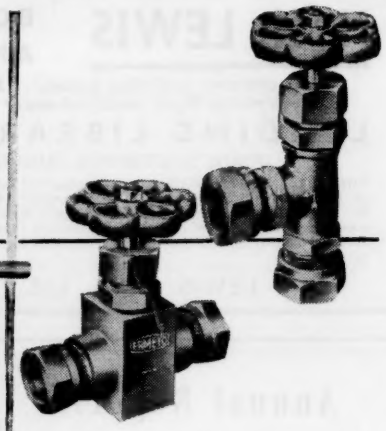
Specialists in Tracing Out-of-Print Books

119-125 CHARING CROSS ROAD, LONDON, W.C.2

GERrard 5660 (16 lines) * Open 9-6 (inc. Sat.)

Two minutes from Tottenham Court Rd. Station

ERMETO
Regd Trade Mark
valves for high-pressure pipe lines



Expressly designed for the job!

Normally our stocks of standard valves are sufficient to meet urgent requirements. For large quantities, however, delivery is from 8-12 weeks. Non-standard valves for special requirements gladly quoted for on receipt of details.

Technical literature available on request

BRITISH ERMETO CORPORATION LTD
Maidenhead, Berks. *Telephone 2271–4*

★ JUST PUBLISHED ★

'THE CRYSTALLINE STATE': VOL. III
Editor: Sir Lawrence Bragg

THE DETERMINATION OF CRYSTAL STRUCTURES

by **H. LIPSON, D.Sc., M.A., F.Inst.P.,** *Head of the Dept. of Physics, Manchester College of Technology, and* **W. COCHRAN, M.A., Ph.D.,** *Lecturer in Physics, University of Cambridge.*

Essentially a practical book on technique covering the subject of crystal-structure determination from the stage at which a set of structure amplitudes has been obtained to the final accurate positioning of the atoms.

CHAPTERS: 1. X-ray Optics. 2. Determination and Use of Space Groups. 3. Calculation of Structure Factors. 4. Summation of Fourier Series. 5. Trial-and-Error Methods. 6. The Use of the Patterson Function. 7. Fourier Methods. 8. Direct Methods. 9. The Accuracy of a Crystal-Structure Determination. Appendices. Indexes.

x + 346 *pages.* 9 *plates.* *Many figures in the text.* 50*s. net*

published by **G. BELL AND SONS, LTD : LONDON**

spence catalysts
Activated Alumina and mixed catalysts, manufactured to customers' individual research and production requirements, form a regular part of the Spence catalyst service. Further details may be obtained on request.
SPENCE
PETER SPENCE & SONS LTD WIDNES LANCS.
ALSO AT LONDON AND BRISTOL

These new Shell products have many important applications in Industry. For example: as SOLVENTS in the manufacture of lacquers, plastics, leathercloth and polishes; as CLEANING AND DEHYDRATING AGENTS in the photographic printing and electroplating trades.

I.P.S.1 specification

PURITY: 99% Isopropyl Alcohol by weight.
SPECIFIC GRAVITY at 20°/20°C: 0.785-0.790.
COLOUR: Water White.
DISTILLATION RANGE (A.S.T.M. D268): Minimum 95%, 81-83°C.
NON-VOLATILE MATTER: Maximum 0.01% weight.

I.P.S.2 specification

PURITY: Minimum 85% Isopropyl Alcohol by weight.
SPECIFIC GRAVITY: at 20°/20°C: 0.815-0.820
COLOUR: Water White.
DISTILLATION RANGE (A.S.T.M. D268): Minimum 95%, 78-81°C.
NON-VOLATILE MATTER: Maximum 0.01% weight.

SHELL

Shell Chemicals Limited, 105-109 Strand, London, W.C.2. Tel: Temple Bar 4455
(DISTRIBUTORS)

Divisional Offices: Walter House, Bedford Street, London, W.C.2. *Tel:* Temple Bar 4455. 42 Deansgate, Manchester, 3. *Tel:* Deansgate 6451. Clarence Chambers, 39 Corporation Street, Birmingham 2. *Tel:* Midland 6954. 28 St. Enoch Square, Glasgow, C.1. *Tel:* Glasgow Central 9561. 53 Middle Abbey Street, Dublin. *Tel:* Dublin 45775. A3

AT REIGATE [redacted]

OUR JOB

AS ESSENCE MANUFACTURERS

IS TO TAKE NATURAL PRODUCTS WHICH HAVE A FLAVOUR OR AROMA OR BOTH; EXTRACT FROM THEM THE PRINCIPLES RESPONSIBLE FOR THAT FLAVOUR AND AROMA, AND THEN PREPARE THESE PRINCIPLES IN SUCH A FORM AS TO BE EASILY AND CONVENIENTLY AND ECONOMICALLY USED BY OUR CUSTOMERS.

WE ARE SPECIALISTS IN THIS FIELD AND CAN OFFER GUARANTEED NATURAL PRODUCTS WHICH FOR QUALITY AND TRUE FLAVOUR ARE IN A CLASS BY THEMSELVES.

REIGATE BRAND—

VANILLA NATURA
GRAPEFRUIT NATURA
ORANGE NATURA
(SWEET OR BITTER)
ORRIS NATURA

WHITE, TOMKINS & COURAGE, LTD.
NORTH ALBERT WORKS, REIGATE

TELEGRAMS: ESSWHITE, REIGATE TELEPHONE: REIGATE 2242-3

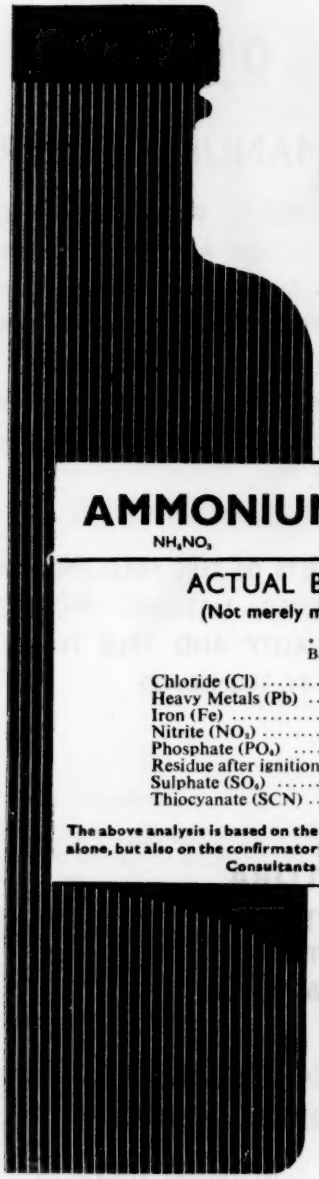
ESTABLISHED 1841

the outstanding purities of

Judactan

analytical reagents

We invite you to compare the actual batch analysis shown here, with the purities guaranteed by the specifications to which you normally work — we are sure the comparison will be helpful to you.



AMMONIUM NITRATE A.R.

NH_4NO_3 Mol. Wt. 80·05

ACTUAL BATCH ANALYSIS

(Not merely maximum impurity values)

Batch No. 50301

Chloride (Cl)	0·0001%
Heavy Metals (Pb)	0·00002%
Iron (Fe)	0·00001%
Nitrite (NO_2)	0·0001%
Phosphate (PO_4)	0·00012%
Residue after ignition	0·004%
Sulphate (SO_4)	0·001%
Thiocyanate (SCN)	0·0007%

The above analysis is based on the results, not of our own Control Laboratories alone, but also on the confirmatory Analytical Certificate issued by independent Consultants of international repute

This is the analysis of a Judactan reagent. And, as with every other reagent in the series it is the *actual batch analysis* — it is one of several of which we are especially proud.

The General Chemical & Pharmaceutical Co. Ltd., Chemical Manufacturers, Judex Works, Sudbury, Middx.

CONTENTS.

PAPERS COMMUNICATED TO THE CHEMICAL SOCIETY.

General, Physical, and Inorganic.

PAGE

Low-temperature Calorimetry and the Thermodynamic Properties of Ethyl Nitrate.
By PETER GRAY and P. L. SMITH 769

Magnetic Susceptibility as measured by Gouy's Method with the Specimen in a Fixed Position.
By O. M. HILAL and G. E. FREDERICKS. 785

The Crystal Structures of the Acid Salts of some Monobasic Acids. Part IV. Ammonium Hydrogen Disalicylate Hydrate.
By T. C. DOWNIE and J. C. SPEAKMAN. 787

Densities of Some Binary Liquid Mixtures. Part II.
By V. S. GRIFFITHS. 860

The Aggregation Tendencies of Acid Wool Dyes in Saline Solutions.
By K. N. DAVIES and J. WHETSTONE 865

Paracyanogen: Its Formation and Properties. Part I.
By L. L. BIRCUMSHAW, F. M. TAYLER, and D. H. WHIFFEN 931

The Effect of Dissolved Oxygen on Diamagnetic Susceptibilities.
By B. C. EGGLESTON, D. F. EVANS, and R. E. RICHARDS 941

Conductimetric Studies in Ketonic Solvents. Part I. Acetone as Solvent.
By J. F. J. DIPPY and S. R. C. HUGHES 953

The Quenching of the Fluorescence of Anthracene. The Transition from Strong to Weak Quenching.
By H. W. MELHUISH and W. S. METCALF 976

The Complex-forming Behaviour of Tin, Germanium, and Titanium with Some Dibasic Carboxylic Acids.
By G. MATTOCK 989

A Dilatometric Study of the Transition in Methyl Alcohol.
By L. A. K. STAVELEY and M. A. P. HOGG 1013

The Halides of Niobium (Columbium) and Tantalum. Part IV. The Electrical Conductivities of Niobium and Tantalum Pentafluorides.
By FRED FAIRBROTHER, WILLIAM C. FRITH, and ALFRED A. WOOLF 1031

The Chromatography of Gases and Vapours. Part III. The Determination of Adsorption Isotherms.
By D. H. JAMES and C. S. G. PHILLIPS 1066

The Preparation of Thorium Alkoxides.
By D. C. BRADLEY, M. A. SAAD, and W. WARDLAW 1091

The Preparation and Some Reactions of Nitryl Fluoride.
By E. E. AYNSLEY, G. HETHERINGTON, and P. L. ROBINSON 1119

The Liquid Dinitrogen Tetroxide Solvent System. Part XVI. Reactions with Ethylammonium Nitrate Solutions: Ethylammonium Tetranitratozincate.
By C. C. ADDISON and N. HODGE 1138

NOTE:

The Liquid Dinitrogen Tetroxide Solvent System. Part XVII. The Equilibrium between Alkylammonium and Nitrosonium Tetranitratozincates.
By C. C. ADDISON, N. HODGE, and R. THOMPSON 1143

Physical Organic.

Kinetics of the Depolymerisation of Paraldehyde in Aqueous Solution.
By R. P. BELL and A. H. BROWN 774

Alkyl–Oxygen Fission in Carboxylic Esters. Part XIII. The Resolution and Reactions of 1 : 2 : 2 : 2-Tetraphenylethanol. Crystalline Solvent Complexes of (+)-1 : 2 : 2 : 2-Tetraphenylethyl Hydrogen Phthalate.
By L. ELLISON and J. KENYON 779

PAGE

Homolytic Aromatic Substitution. Part V. Partial Rate Factors for the Phenylation of Diphenyl.
By J. I. G. CADOGAN, D. H. HEY, and GARETH H. WILLIAMS 794

A Characteristic Infra-red Absorption of the Triphenylmethyl Group.
By S. PINCHAS and DAVID SAMUEL 863

Addition of Free Radicals to Unsaturated Systems. Part VII. 1 : 1-Difluoroethylene.
By R. N. HASZELDINE and B. R. STEELE 923

The Thermal Oxidation of Hydrazine Vapour.
By W. I. H. WINNING 926

The Photochemical Autoxidation of *iso*Propylbenzene.
By H. W. MELVILLE and S. RICHARDS 944

Acid-catalysed Racemisation of 1-Methylheptyl Acetate.
By M. P. BALFE, W. H. F. JACKMAN, and J. KENYON 965

A Kinetic Study of the Formation and Hydrolysis of *tert.*-Butyl Hypochlorite.
By M. ANBAR and I. DOSTROVSKY 1094

Ultra-violet Absorption Spectra of Some Organic Hypohalites.
By M. ANBAR and I. DOSTROVSKY 1105

An Electrochemical Study of Salmine Salts.
By C. W. DAVIES and G. H. NANCOLLAS 1112

The Oxidation of Phenylhydrazones. Part II.
By B. M. LYNCH and K. H. PAUSACKER 1131

NOTE:

A Statistical Study of Some Olefinic Absorption Bands in the Infra-red Region.
By R. L. WERNER and P. D. LARK 1152

Organic.

Cyclisation of Arylbutyric Acids with Polyphosphoric Acid. The By-products.
By R. F. EVANS and J. C. SMITH 798

Studies in the Steroid Group. Part LXVII. Infra-red Absorption of Disubstituted *cis*Ethylenic Centres.
By H. B. HENBEST, G. D. MEAKINS, and GEOFFREY W. WOOD 800

The Galactan of *Strychnos nux-vomica* Seeds.
By P. ANDREWS, L. HOUGH, and J. K. N. JONES 806

Studies in Stereochemical Structure. Part X. Optically Active Desyl Chloride.
By ROBERT ROGER and ROBERT WOOD 811

Elimination of Water from Glycols. Dehydration of Racemic 1 : 4-Glycols Derived from Acenaphthene.
By ROBERT ROGER and DAVID M. SHEPHERD 812

The Isomerisation of Unsaturated Steroids in Liquid Suphur Dioxide.
By A. W. D. HUDGELL, J. H. TURNBULL, and WALTER WILSON 814

Derivatives of Acetoacetic Acid. Part I. The Reaction of Diketen with 1 : 2- and 1 : 3-Ketols to give γ- and δ-Lactones.
By R. N. LACEY 816

Derivatives of Acetoacetic Acid. Part II. The Rearrangement of 3-Acyl-2 : 5-dihydrofuran-2-one Derivatives to Furan-3-carboxylic Acids.
By R. N. LACEY. 822

Derivatives of Acetoacetic Acid. Part III. The Pyrolysis of Acetoacetates of Ethynylcarbinols.
By R. N. LACEY 827

Derivatives of Acetoacetic Acid. Part IV. A New Route to α-Acetyltetronic Acids.
By R. N. LACEY 832

Derivatives of Acetoacetic Acid. Part V. The Reaction of Diketen with Thioureas, Amidines, Guanidines, and *S*-Substituted Thioureas.
By R. N. LACEY 839

Derivatives of Acetoacetic Acid. Part VI. A Synthesis of 1 : 3-Oxazine Derivatives employing Diketen.
By R. N. LACEY 845

Derivatives of Acetoacetic Acid. Part VII. α-Acetyltetramic Acids.
By R. N. LACEY 850

Derivatives of Acetoacetic Acid. Part VIII. The Synthesis of Coumarins from Aryl Acetoacetates.
By R. N. LACEY 854

PAGE

The Preparation of 2-Substituted Fluoranthenes.
By Neil Campbell and J. F. K. Wilshire 867

3 : 6-Disubstituted Fluorenes. Part II. The Preparation of 3 : 6-Diaminofluorene from Fluorene, and the Attempted Internuclear Cyclisation of Derivatives of 4 : 4′-Diaminodiphenylmethane
By A. Barker and C. C. Barker 870

Diacid Bases. Part II. Curarising Agents. Derivatives of Diphenyl Ether.
By A. R. Brown and F. C. Copp 873

Organometallic and Organometalloidal Compounds. Part VIII. Properties of Trifluoromethyl Arsenic Acids and of Other Fluorine-containing Acids.
By H. J. Emeléus, R. N. Haszeldine, and Ram Chand Paul 881

Triterpenoids. Part XV. The Constitution of Icterogenin, a Physiologically Active Triterpenoid.
By D. H. R. Barton and P. de Mayo 887

Triterpenoids. Part XVI. The Constitution of Rehmannic Acid.
By D. H. R. Barton and P. de Mayo 900

Triterpenoids. Part XVII. The Transformation of Lanostadienol (Lanosterol) into 14-Methylcholestan-3β-ol.
By D. H. R. Barton, D. A. J. Ives, and B. R. Thomas 903

The Conversion of Hecogenin Acetate into 11-Oxotigogenin Acetate.
By J. W. Cornforth, J. M. Osbond, and G. H. Phillipps 907

Reactions of Fluorocarbon Radicals. Part XIII. Alternative Syntheses, Properties, and Spectra of Trifluoro-nitroso- and -nitro-methane.
By J. Jander and R. N. Haszeldine 912

Reactions of Fluorocarbon Radicals. Part XIV. Hexafluoroazoxymethane.
By J. Jander and R. N. Haszeldine 919

Synthesis of 9 : 18-Diaza*iso*violanthrone.
By J. King and G. R. Ramage 936

Organosilicon Compounds. Part VIII. The (Trimethylsilylmethyl)benzoic Acids.
By C. Eaborn and S. H. Parker 939

Steroids. Part VII. Some 5-Hydroxy-derivatives of Cholestane.
By A. J. Fudge, C. W. Shoppee, and G. H. R. Summers 958

The Constitution of Conessine. Part VII. Degradation of Some Reduced Quinoline and Indole Bases.
By B. Bailey, R. D. Haworth, and J. McKenna 967

The Oxidation of Some Aromatic Amines with Persulphate.
By E. Boyland and Peter Sims 980

Triphenylmethane Derivatives from Condensations of Phenols with Hydroxybenzaldehydes.
By J. E. Driver and J. B. Sousa 985

Reactions of 4-Thionchromones with Amino-compounds, and with Methyl Iodide.
By Wilson Baker, G. G. Clarke, and J. B. Harborne 998

Constituents of the Lipids of Tubercle Bacilli. Part II.
By J. D. Chanley and N. Polgar 1003

Constituents of the Lipids of Tubercle Bacilli. Part III. Mycolipenic Acid.
By N. Polgar 1008

Constituents of the Lipids of Tubercle Bacilli. Part IV. Mycoceranic Acid.
By N. Polgar 1011

Synthetic Antimalarials. Part XLIX. The Structure and Synthesis of the Dihydrotriazine Metabolite of Proguanil.
By H. C. Carrington, A. F. Crowther, and G. J. Stacey 1017

Halogenated *o*- and *p*-Phenolic Ketones.
By Ng. Ph. Buu-Hoï, Ng. D. Xuong, and Denise Lavit 1034

Syntheses from Phthalimido-acids. Part IV. *p*-Glycylaminobenzoic Acid and Derivatives.
By F. E. King, J. W. Clark-Lewis, D. A. A. Kidd, and G. R. Smith . . . 1039

Syntheses from Phthalimido-acids. Part V. Amides of Glycine, dl-Alanine and l-Glutamic Acid with Amphetamine, Benzocaine, and Procaine.
By F. E. King, J. W. Clark-Lewis, and G. R. Smith 1044

PAGE

Syntheses from Phthalimido-acids. Part VI. Further Products from Phthalyl-DL-aspartic Anhydride, and the Preparation of Phthalylglycyl-DL-asparagine and -DL-serine.
By F. E. KING, J. W. CLARK-LEWIS, and G. R. SMITH 1046

Polycyclic Systems. Part VI. 8-*meso*-α-Naphthanthr-10-one and 2 : 3-8 : 9-Dibenzoperylene.
By E. A. BRAUDE, J. S. FAWCETT, and A. A. WEBB 1049

Tropolones. Part VIII. Synthesis and Properties of 7-Hydroxybenzo*cyclo*heptatrien-3-one.
By G. L. BUCHANAN 1060

The β-Phenylserine Series. Part III.
By ERNST D. BERGMANN, H. BENDAS, and E. KRAKAUER 1064

Further Investigations of Trifluoromethyldiphenyl Derivatives.
By M. R. PETTIT and J. C. TATLOW 1071

Phthalaldehydes and Related Compounds. Part IV. Synthesis of Gladiolic Acid.
By J. J. BROWN and G. T. NEWBOLD 1076

Organometallic Compounds of the Alkali Metals. Part III. Metallation of Alkylbenzenes by Alkyl-sodium and -potassium Compounds. The Character of Aromatic Metallation Reactions.
By D. BRYCE-SMITH 1079

The Chemistry of Polymerised Oils. Part IV. Thermal Polymerisation of Some Long-chain Unsaturated Fatty Esters.
By A. L. CLINGMAN, D. E. A. RIVETT, and DONALD A. SUTTON 1088

Aromatic Hydrocarbons. Part LXVI. Di*peri*naphthyleneanthracenes.
By E. CLAR, W. KELLY, and (in part) J. W. WRIGHT 1108

Quaternary Ammonium Salts. Part IV. Hydrolysis of the Nitrile Group before Decomposition of the Quaternary Ammonium Group. Preparation and Decomposition of Some Quaternary Ammonium Salts.
By WADIE TADROS and ALFY BADIE SAKLA 1116

Reactions of Thiols and Thioethers. Part I. An Analogue of the Mannich Reaction involving Thiols, Formaldehyde, and Active Methylene or Methylidyne Compounds.
By F. POPPELSDORF and S. J. HOLT 1124

ortho-Hydroxylation of Phenols. Part IV. Pyrogallols.
By J. D. LOUDON and L. A. SUMMERS 1134

NOTES:

Crystalline 2 : 4-Di-*O*-methyl-D-glucose.
By D. J. BELL and D. J. MANNERS 1145

Crystalline 1-*O*-Methyl-D-fructose.
By S. BAYNE and JENNIFER WILDY 1147

Some Phosphorus-containing Derivatives of 2 : 2 : 2-Trichloroethanol.
By W. GERRARD, W. J. GREEN, and R. J. PHILLIPS 1148

The Preparation of β-*p*-Hydroxyphenyl-α-mercaptopropionic Acid and Some Related Acids, and the Action of Tyrosinase on the Former.
By D. G. BEW and G. R. CLEMO 1150

A Novel Method of Cyanoethylation. Part II. 10-2′-Cyanoethyl-9 : 10-dihydrophenanthridine.
By R. J. BATES and J. CYMERMAN-CRAIG 1153

Preparation of Pentachlorothiophenol and Some Other Sulphur Compounds.
By WADIE TADROS and EZZAT SAAD 1155

2-Acetoacetyl-4-methylphenol as a Reagent for Primary Amines.
By J. B. HARBORNE and A. S. WEAVING 1157

5-Aminoindole.
By JOHN HARLEY-MASON and A. H. JACKSON 1158

Synthesis of 2-Chloro-6-methylphenoxyacetic Acid.
By J. H. BARNES and P. G. MARSHALL 1159

2 : 6-Bis-2′-hydroxyethylnaphthalene.
By MORTON MEADOW and WILSON M. WHALEY 1161

Some Derivatives of Phenanthrene.
By MORTON MEADOW and WILSON M. WHALEY 1162

3 : 6-Dicyanocatechol.
By J. D. LOUDON and D. K. V. STEEL 1163

INDEX OF AUTHORS' NAMES.

Addison, C. C., and Hodge, N., 1138.
Addison, C. C., Hodge, N., and Thompson, R., 1143.
Anbar, M., and Dostrovsky, I., 1094, 1105.
Andrews, P., Hough, L., and Jones, J. K. N., 806.
Aynsley, E. E., Hetherington, G., and Robinson, P. L., 1119.
Bailey, B., Haworth, R. D., and McKenna, J., 967.
Baker, W., Clarke, G. G., and Harborne, J. B., 998.
Balfe, M. P., Jackman, W. H. F., and Kenyon, J., 965.
Barker, A., and Barker, C. C., 870.
Barker, C. C. See Barker, A., 870.
Barnes, J. H., and Marshall, P. G., 1159.
Barton, D. H. R., and de Mayo, P., 887, 900.
Barton, D. H. R., Ives, D. A. J., and Thomas, B. R., 903.
Bates, R. J., and Cymerman-Craig, J., 1153.
Bayne, S., and Wildy, J., 1147.
Bell, D. J., and Manners, D. J., 1145.
Bell, R. P., and Brown, A. H., 774.
Bendas, H. See Bergmann, E. D., 1064.
Bergmann, E. D., Bendas, H., and Krakauer, E., 1064.
Bew, D. G., and Clemo, G. R., 1150.
Bircumshaw, L. L., Tayler, F. M., and Whiffen, D. H., 931.
Boyland, E., and Sims, P., 980.
Bradley, D. C., Saad, M. A., and Wardlaw, W., 1091.
Braude, E. A., Fawcett, J. S., and Webb, A. A., 1049.
Brown, A. H. See Bell, R. P., 774.
Brown, A. R., and Copp, F. C., 873.
Brown, J. J., and Newbold, G. T., 1076.
Bryce-Smith, D., 1079.
Buchanan, G. L., 1060.
Buu-Hoï, Ng. Ph., Xuong, Ng. D., and Lavit, D., 1034.
Cadogan, J. I. G., Hey, D. H., and Williams, G. H., 794.
Campbell, N., and Wilshire, J. F. K., 867.
Carrington, H. C., Crowther, A. F., and Stacey, G. J., 1017.
Chanley, J. D., and Polgar, N., 1003.
Clar, E., Kelly, W., and Wright, J. W., 1108.
Clarke, G. G. See Baker, W., 998.
Clark-Lewis, J. W. See King, F. E., 1039, 1044, 1046.
Clemo, G. R. See Bew, D. G., 1150.
Clingman, A. L., Rivett, D. E. A., and Sutton, D. A., 1088.
Copp, F. C. See Brown, A. R., 873.
Cornforth, J. W., Osbond, J. M., and Phillipps, G. H., 907.
Crowther, A. F. See Carrington, H. C., 1017.
Cymerman-Craig, J. See Bates, R. J., 1153.
Davies, C. W., and Nancollas, G. H., 1112.
Davies, K. N., and Whetstone, J., 865.
de Mayo, P. See Barton, D. H. R., 887, 900.
Dippy, J. F. J., and Hughes, S. R. C., 953.
Dostrovsky, I. See Anbar, M., 1094, 1105.
Downie, T. C., and Speakman, J. C., 787.
Driver, J. E., and Sousa, J. B., 985.
Eaborn, C., and Parker, S. H., 939.
Eggleston, B. C., Evans, D. F., and Richards, R. E., 941.
Ellison, L., and Kenyon, J., 779.
Emeléus, H. J., Haszeldine, R. N., and Paul, R. C., 881.
Evans, D. F. See Eggleston, B. C., 941.
Evans, R. F., and Smith, J. C., 798.
Fairbrother, F., Frith, W. C., and Woolf, A. A., 1031.
Fawcett, J. S. See Braude, E. A., 1049.
Fredericks, G. E. See Hilal, O. M., 785.
Frith, W. C. See Fairbrother, F., 1031.
Fudge, A. J., Shoppee, C. W., and Summers, G. H. R., 958.
Gerrard, W., Green, W. J., and Phillips, R. J., 1148.
Gray, P., and Smith, P. L., 769.
Green, W. J. See Gerrard, W., 1148.
Griffiths, V. S., 860.
Harborne, J. B., and Weaving, A. S., 1157.
Harborne, J. B. See also Baker, W., 998.
Harley-Mason, J., and Jackson, A. H., 1158.
Haszeldine, R. N., and Steele, B. R., 923.
Haszeldine, R. N. See also Emeléus, H. J., 881, and Jander, J., 912, 919.
Haworth, R. D. See Bailey, B., 967.
Henbest, H. B., Meakins, G. D., and Wood, G. W., 800.
Hetherington, G. See Aynsley, E. E., 1119.
Hey, D. H. See Cadogan, J. I. G., 794.
Hilal, O. M., and Fredericks, G. E., 785.
Hodge, N. See Addison, C. C., 1138, 1143.
Hogg, M. A. P. See Staveley, L. A. K., 1013.
Holt, S. J. See Poppelsdorf, F., 1124.
Hough, L. See Andrews, P., 806.
Hudgell, A. W. D., Turnbull, J. H., and Wilson, W., 814.
Hughes, S. R. C. See Dippy, J. F. J., 953.
Ives, D. A. J. See Barton, D. H. R., 903.
Jackman, W. H. F. See Balfe, M. P., 965.
Jackson, A. H. See Harley-Mason, J., 1158.
James, D. H., Phillips, C. S. G., 1066.
Jander, J., and Haszeldine, R. N., 912, 919.
Jones, J. K. N. See Andrews, P., 806.
Kelly, W. See Clar, E., 1108.
Kenyon, J. See Balfe, M. P., 965, and Ellison, L., 779.
Kidd, D. A. A. See King, F. E., 1039.
King, F. E., Clark-Lewis, J. W., Kidd, D. A. A., and Smith, G. R., 1039.
King, F. E., Clark-Lewis, J. W., and Smith, G. R., 1044, 1046.
King, J., and Ramage, G. R., 936.
Krakauer, E. See Bergmann, E. D., 1064.
Lacey, R. N., 816, 822, 827, 832, 839, 845, 850, 854.
Lark, P. D. See Werner, R. L., 1152.
Lavit, D. See Buu-Hoï, Ng. Ph., 1034.
Loudon, J. D., and Steel, D. K. V., 1163.
Loudon, J. D., and Summers, L. A., 1134.
Lynch, B. M., and Pausacker, K. H., 1131.
McKenna, J. See Bailey, B., 967.
Manners, D. J. See Bell, D. J., 1145.
Marshall, P. G. See Barnes, J. H., 1159.
Mattock, G., 989.
Meadow, M., and Whaley, W. M., 1161, 1162.
Meakins, G. D. See Henbest, H. B., 800.
Melhuish, H. W., and Metcalf, W. S., 976.
Melville, H. W., and Richards, S., 944.
Metcalf, W. S. See Melhuish, H. W., 976.
Nancollas, G. H. See Davies, C. W., 1112.

Newbold, G. T. See Brown, J. J., 1076.
Osbond, J. M. See Cornforth, J. W., 907.
Parker, S. H. See Eaborn, C., 939.
Paul, R. C. See Emeléus, H. J., 881.
Pausacker, K. H. See Lynch, B. M., 1131.
Pettit, M. R., and Tatlow, J. C., 1071.
Phillipps, G. H. See Cornforth, J. W., 907.
Phillips, C. S. G. See James, D. H., 1066.
Phillips, R. J. See Gerrard, W., 1148.
Pinchas, S., and Samuel, D., 863.
Polgar, N., 1008, 1011.
Polgar, N. See also Chanley, J. D., 1003.
Poppelsdorf, F., and Holt, S. J., 1124.
Ramage, G. R. See King, J., 936.
Richards, R. E. See Eggleston, B. C., 941.
Richards, S. See Melville, H. W., 944.
Rivett, D. E. A. See Clingman, A. L., 1088.
Robinson, P. L. See Aynsley, E. E., 1119.
Roger, R., and Shepherd, D. M., 812.
Roger, R., and Wood, R., 811.
Saad, E. See Tadros, W., 1155.
Saad, M. A. See Bradley, D. C., 1091.
Sakla, A. B. See Tadros, W., 1116.
Samuel, D. See Pinchas, S., 863.
Shepherd, D. M. See Roger, R., 812.
Shoppee, C. W. See Fudge, A. J., 958.
Sims, P. See Boyland, E., 980.
Smith, G. R. See King, F. E., 1039, 1044, 1046.
Smith, J. C. See Evans, R. F., 798.
Smith, P. L. See Gray, P., 769.
Sousa, J. B. See Driver, J. E., 985.
Speakman, J. C. See Downie, T. C., 787.
Stacey, G. J. See Carrington, H. C., 1017.
Staveley, L. A. K., and Hogg, M. A. P., 1013.
Steel, D. K. V. See Loudon, J. D., 1163.
Steele, B. R. See Haszeldine, R. N., 923.
Summers, G. H. R. See Fudge, A. J., 958.
Summers, L. A. See Loudon, J. D., 1134.
Sutton, D. A. See Clingman, A. L., 1088.
Tadros, W., and Saad, E., 1155.
Tadros, W., and Sakla, A. B., 1116.
Tatlow, J. C. See Pettit, M. R., 1071.
Tayler, F. M. See Bircumshaw, L. L., 931.
Thomas, B. R. See Barton, D. H. R., 903.
Thompson, R. See Addison, C. C., 1143.
Turnbull, J. H. See Hudgell, A. W. D., 814.
Wardlaw, W. See Bradley, D. C., 1091.
Weaving, A. S. See Harborne, J. B., 1157.
Webb, A. A. See Braude, E. A., 1049.
Werner, R. L., and Lark, P. D., 1152.
Whaley, W. M. See Meadow, M., 1161, 1162.
Whetstone, J. See Davies, K. N., 865.
Whiffen, D. H. See Bircumshaw, L. L., 931.
Wildy, J. See Bayne, S., 1147.
Williams, G. H. See Cadogan, J. I. G., 794.
Wilshire, J. F. K. See Campbell, N., 867.
Wilson, W. See Hudgell, A. W. D., 814.
Winning, W. I. H., 926.
Wood, G. W. See Henbest, H. B., 800.
Wood, R. See Roger, R., 811.
Woolf, A. A. See Fairbrother, F., 1031.
Wright, J. W. See Clar, E., 1108.
Xuong, Ng. D. See Buu-Hoï, Ng. Ph., 1034.

NOTICES TO AUTHORS OF PAPERS

Scientific communications for the *Journal* should be addressed to " The Honorary Secretaries, The Chemical Society, Burlington House, London, W.1." Papers to be read before a meeting of the Society are selected by the Honorary Secretaries.

A paper is not normally considered for publication in the *Journal* unless at least one of the authors is a Fellow of the Society, but in exceptional circumstances the Council is prepared to consider papers submitted by non-Fellows.

Communications that have appeared or have been accepted for publication with essentially the same scientific content in another Journal or freely available printed work shall not be published in the *Journal* of the Society unless this course is approved by the Council.

Papers are accepted by the Society on the understanding that the authors have obtained any necessary authority to publish.

The Society reserves the right to retain all papers sent to it, and authors are therefore advised to keep copies. When papers have been accepted for publication the authors are not at liberty, save by permission of the Council, to withdraw or delay them, or to publish them elsewhere until they have appeared in the *Journal* of the Society. Papers which are retained by the Council after being judged unsuitable for publication in the *Journal* are deposited in the Archives of the Society; this right is not usually exercised in regard to illustrations.

Authors are solely responsible for the factual accuracy of their papers. They are particularly requested to verify references.

Authors are requested to see that their papers conform, as nearly as possible, to the normal conventions of the *Journal*. It is essential that drawings and photographs be presented in the style required by the Society. Every paper must be prefaced by a short summary, but " Notes " do not require a summary. Authors should consult the brochure entitled " The Presentation of Papers for the Journal of the Chemical Society " for detailed instructions and advice on these and cognate matters; Fellows of the Society are entitled to one copy each, gratis, on application to the General Secretary, The Chemical Society, Burlington House, London, W.1; further copies may be obtained at the public price which is 1*s.* 6*d.* each, post free, or 12*s.* 6*d.* per 10 copies, post free.

Authors are expected to be familiar with the normal rules of nomenclature, but are invited to communicate with the Editor if in doubt or in special cases. Some of the principles followed are reviewed in " Modern Chemical Nomenclature," by Dr. Clarence Smith (*J.*, 1936, 1067) (6*d.* post free), and in the Editorial Reports on Nomenclature (*J.*, 1950, 3699; 1951, 3515; 1952, 5057) (1*s.* each post free). Much valuable discussion will be found in " British Chemical Nomenclature," by Dr. A. D. Mitchell [Edward Arnold and Co., 1948]. Authors should choose their symbols from the " Report by the Symbols Committee of the Royal Society representing the Royal Society, the Chemical Society, the Faraday Society, and the Physical Society, 1951 " (*J.*, 1951, 1677) [9*d.* per copy or 12*s.* per 25 copies (post free), obtainable from the General Secretary, The Chemical Society].

Authors will be expected to pay the cost of any considerable changes made by them in proof, apart from the correction of printers' errors.

Each author, or joint author, receives 10 preprints (without covers) free of charge. A quotation for extra preprints and an order form will be sent with the proofs. The order form (and any necessary remittance) must be returned with the proofs and the MS. to the Editor.

INFORMATION FOR CANDIDATES FOR FELLOWSHIP

The Chemical Society was founded in 1841 and received a Royal Charter in 1848.

The main function of the Society is to foster original research in chemistry and to facilitate the discussion and dissemination of new knowledge in all branches of the science.

Fellowship of the Society is open to men and women of all nationalities who are interested in chemistry and wish to keep in touch with its advances. Fellows are elected by the Council.

PRIVILEGES

Fellows paying the Annual Subscription of £4 10*s*. have the following privileges:

To receive a selection of the publications of the Society to a value of £3 0*s*. without further payment.

To purchase additional publications at favourable prices.

To attend all meetings, discussions and lectures of the Society and to introduce two guests.

To consult and borrow books in the Library. Books may be borrowed by post.

To apply for grants from the Research Fund.

To submit papers for publication in the *Journal*.

Fellows under 27 years of age may pay £1 15*s*. per annum and receive:

The *Proceedings*, *Annual Reports on the Progress of Chemistry*, and *Quarterly Reviews* without further payment.

The right to purchase other publications at favourable prices.

All the other privileges of Fellowship.

LIBRARY

The extensive reference and lending library of the Chemical Society contains over 50,000 volumes dealing with every aspect of chemistry and with many branches of related sciences. The library is open on Monday to Friday from 10 a.m. to 9 p.m., and on Saturdays from 10 a.m. to 5 p.m.

Books available on loan may be sent by post to Fellows residing in Great Britain or Ireland.

MEETINGS

(*a*) *In London.*—Scientific Meetings of the Society are usually held on two Thursdays in each month from October to June at Burlington House, at which papers dealing with original work are read and discussed, organised discussions on subjects of current interest are arranged, and lectures by eminent British and foreign chemists are delivered.

(*b*) *Outside London.*—Scientific Meetings and lectures arranged by the Society's Local Representatives are also held outside London, and form an important part of the activities of the Society.

RESEARCH FUND

A Research Fund is available for the assistance of chemical research, and sums amounting annually to about £700 are granted for this purpose. Application for grants must be made on the appropriate form, which may be obtained from the General Secretary.

A brochure describing the activities of the Society and forms of application for Fellowship can be obtained from The General Secretary, The Chemical Society, Burlington House, Piccadilly, London, W.1.

Low-temperature Calorimetry and the Thermodynamic Properties of Ethyl Nitrate.

By PETER GRAY and P. L. SMITH.

[Reprint Order No. 4580.]

The molar heat capacity C_p of ethyl nitrate has been measured from 20° to 293° K. The m. p. is 178·6° K. On fusion, C_p increases from 27·3 to 38·7 cal. deg.$^{-1}$ mole^{-1}; at 298° K C_p is 40·7. The enthalpy and entropy differences between absolute zero and 298° K (standard state) are 9240 cal. mole^{-1} and 59·08 cal. deg.$^{-1}$ mole^{-1}, respectively.

Existing values of the heat of formation of ethyl nitrate are discussed and a critical selection made of $\Delta H_f^\circ = -45{\cdot}8 \pm 0{\cdot}8$ kcal. mole^{-1} (liquid). The standard entropy of formation is $-118{\cdot}1$ cal. deg.$^{-1}$ mole^{-1} and the standard free energy of formation $-\Delta F_f^\circ$ is $-10{\cdot}61$ kcal. mole^{-1}.

The equilibrium constant $K = [C_2H_5{\cdot}NO_3][H_2O]/[C_2H_5{\cdot}OH][HNO_3]$ of esterification by pure reactants is $4{\cdot}8 \times 10^4$ and the heat liberated $-\Delta H_{est}$ is 6·4 kcal. mole^{-1}. In aqueous solution heat is absorbed ($\Delta H'_{est} = 3{\cdot}1$ kcal. mole^{-1}), the free-energy balance is unfavourable, and the equilibrium constant K' is $5{\cdot}8 \times 10^{-2}$. Similar differences were found for methyl nitrate by Gray and Smith (*J.*, 1953, 2380).

OWING to the explosive character of organic nitrates and the complexity of their decomposition (Gray and Yoffe, *Proc. Roy. Soc.*, 1949, *A*, **200**, 114), the thermodynamic properties of many of them have not been measured, and recorded values of their heats of formation are often discordant.

For the simplest members of the series, methyl and ethyl nitrates, values are available for their heat of formation. To enable free energies of formation, entropies of formation, and equilibrium constants of reactions in which these esters take part to be determined, further data are necessary. These have recently been provided for methyl nitrate by Gray and Smith (*J.*, 1953, 2380). In order to supply similar information for ethyl nitrate, direct measurements have been made of its specific heat from temperatures near the absolute zero to room temperature. The corresponding entropy and enthalpy differences have been evaluated from these and from the latent heat of fusion. The results have been used in calcuations of the heat of formation at absolute zero, the heat of formation of gaseous atoms, the standard free energy of formation, and in applications of these to equilibria. The properties of methyl and ethyl nitrate are compared.

EXPERIMENTAL.

Materials.—Pure ethyl nitrate, supplied by the Explosives Research & Development Establishment, Waltham Abbey, was dried ($CaCl_2$) and fractionally distilled; the middle fraction had b. p. 89°/760 mm.

Apparatus and Method.—For work below 120° K, these are substantially identical with those described by Gray and Smith (*loc. cit.*). However, because of the large heat capacity, to improve thermal couplings between the thermometers and the sample, measurements of thermal capacities above 120° K were made by winding the heating coil and thermometers directly on to the copper can containing the ethyl nitrate. Correction for the heat capacity of the can and the copper shavings present to ensure rapid distribution of heat was computed from published data on copper (*e.g.*, Giauque and Meads, *J. Amer. Chem. Soc.*, 1941, **63**, 1897).

Results.—Melting point. Ethyl nitrate melted sharply at 178·6° K (cf. $MeNO_3$, 190·2° K). The value recorded in tables (−102° C) is 7·5° low.

Latent heat and entropy of fusion. The enthalpy of fusion L_f at 178° K was determined from measurements of the amount of heat required to convert solid a little below the m. p. into liquid a little above it. Corrections were made for heat capacities and radiation losses.

Molar latent heat of fusion $L_f = 2038 \pm 42$ cal.
Molar entropy of fusion $S_f = 11{\cdot}41 \pm 0{\cdot}21$ cal. deg.$^{-1}$

Heat capacity. Table 1 gives the experimental values of the molar heat capacities C_p in cal. deg.$^{-1}$ measured from 20° to 293° K. From its value at very low temperatures C_p increases continuously up to 27·3 cal. deg.$^{-1}$ mole^{-1} at T_f. No other transitions are observed. Above the m. p., C_p for the liquid increases slowly from 38·7 at T_f to 40·7 cal. deg.$^{-1}$ mole^{-1} at 298° K.

TABLE 1. *Molar heat capacity* C_p *of ethyl nitrate.* (*Measured values.*)

Temp. (K)	C_p *	Temp. (K)	C_p	Temp. (K)	C_p	Temp. (K)	C_p	Temp. (K)	C_p	Temp. (K)	C_p
Series I: 0·3316 mole.				Series II: 0·3103 mole.							
21·6°	3·80	51·6°	10·30	91·3°	15·9	128°	19·1	178·6° †	—	220°	39·0
22·3	4·25	62·7	12·12	92·1	15·6	134	19·1	182	38·9	223	39·0
26·1	4·98	67·3	13·00	93·8	16·2	146	20·3	188	38·8	244	40·0
29·2	5·75	77·7	13·60	105·9	16·2	151	20·9	191	39·1	249	39·8
39·0	8·30	81·5	14·4	107·2	16·5	159	21·2	198	39·1	260	40·3
42·5	8·42	84·7	14·6	121	17·9	167	21·8	200	40·0	270	40·4
44·7	9·11	87·1	14·8	124	18·4	169	22·7	208	39·7	280	40·8
48·3	9·50			125	18·0	175	23·4	209	40·0	293	40·0

* C_p is in cal. deg.$^{-1}$ mole^{-1} throughout. † M. p.

These values of C_p are plotted against T. From the smoothed graph obtained (see Figure) values of C_p and of C_p/T were derived. These values are listed in Table 2 and are used in calculations of thermodynamic functions.

TABLE 2. *Molar heat capacity of ethyl nitrate. Interpolated values of* C_p *and* C_p/T *and derived thermodynamic functions* (*see Figure*).

Temp. (K)	C_p *	C_p/T †	Enthalpy diff., ‡ $H(T)-H(0)$	"Absolute entropy," * $S(T)-S(0)$	Temp. (K)	C_p *	C_p/T †	Enthalpy diff., ‡ $H(T)-H(0)$	"Absolute entropy," * $S(T)-S(0)$
Solid ethyl nitrate					160°	21·50	0·134	2030	24·83
15°	1·50	0·100	5·60	0·50	170	22·45	0·132	—	—
20	3·32	0·166	18·8	1·17	178·6 §	23·3	0·130	2445	27·27
25	4·85	0·194	—	—					
30	6·10	0·203	—	—	*Liquid ethyl nitrate*				
35	7·24	0·207	—	—	178·6	38·75	0·217	4485	38·68
40	8·14	0·203	138	5·12	180	38·8	0·216	—	—
45	9·00	0·200	—	—	190	39·1	0·205	—	—
50	9·96	0·199	—	—	200	39·2	0·196	5320	43·11
60	11·72	0·195	337	9·10	210	39·4	0·188	—	—
70	13·10	0·187	—	—	220	39·6	0·180	6110	46·87
80	14·25	0·178	598	12·83	230	39·75	0·173	—	—
90	15·29	0·170	—	—	240	39·9	0·166	6904	50·33
100	16·17	0·162	903	16·13	250	40·05	0·160	—	—
110	17·00	0·154	—	—	260	40·2	0·155	7705	53·54
120	17·95	0·149	1245	19·21	270	40·4	0·150	—	—
130	18·93	0·146	—	—	280	40·5	0·145	8510	56·54
140	19·68	0·141	1620	22·06	290	40·6	0·140	—	—
150	20·72	0·138	—	—	291	40·6	0·140	8960	58·11
					298	40·7	0·137	9240	59·08

* In cal. deg.$^{-1}$ mole^{-1}. † In cal. deg.$^{-2}$ mole^{-1}. ‡ In cal. mole^{-1}.
§ M. p.: $L_f = 2038$ cal. mole^{-1}; $S_f = 11{\cdot}41$ cal. deg.$^{-1}$ mole^{-1}.

TABLE 3. *Calculation of molar enthalpy* (*cal. mole*$^{-1}$) *of ethyl nitrate relative to absolute zero.*

Debye's T^3 law, 0—15° K	5·60
Graphical integration, 15—178·6° K	2442
Fusion at 178·6° K	2038
Graphical integration, 178·6—298° K	4756
Total $H(298)-H(0)$	9242

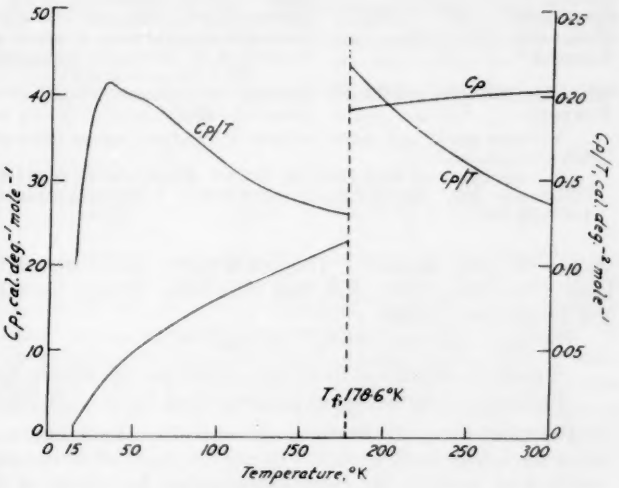
TABLE 4. *Calculation of the molar entropy* (*cal. deg.*$^{-1}$) *of ethyl nitrate relative to absolute zero* ("*absolute entropy*").

Debye's T^3 law, 0—15° K	0·50
Graphical integration, 15—178·6° K	26·77
Fusion, 2038/178·6	11·41
Graphical integration, 178·6—298° K	20·40
Total $S_{abs.}°$ (298)	59·08

Difference between molar heat content at room temperature and at absolute zero. Calculation of the enthalpy difference between 0° and 298·1° K (shown in Table 3) is made partly from numerical integration on the assumption that Debye's T^3 law holds below 15° K, and the remainder from the latent-heat term and a graphical integration of the curve between the C_p curve and the T axis. The difference in molar enthalpy between 0° and 298·1° K is 9240 cal.

Entropy from calorimetric data. Table 4 summarizes an entropy calculation, which is made partly from Debye's T^3 law, partly from graphical integration above and below the m. p., and from the measured entropy of fusion.

Molar heat capacity of ethyl nitrate 15° K to 300° K.



Discussion

These properties of ethyl nitrate may be compared with those recently reported for methyl nitrate by Gray and Smith. They enable values to be derived of the enthalpy, entropy, and free energy of formation under different conditions and to be applied to the reactions of ethyl nitrate.

Physical Properties of Ethyl Nitrate.—Ethyl nitrate melts at 178·6° K ($T_f = -94·6°$ C). The first determination of T_f was made by von Schneider (*Z. physikal. Chem.*, 1897, **22**, 233), who measured temperatures on an iron–constantan thermocouple and found $T_f = -112°$ C. The corrected value given by Timmermans (I.C.T., McGraw Hill, New York, 1927, Vol. I, 306) is −102° C. Errors in these early determinations may be due to glass formation and supercooling. The increase of specific heat at the m. p. from 27·3 for the solid to 38·7 (cal. deg.$^{-1}$ mole^{-1}) for the liquid indicates that other modes of motion as well as translation have come into play. The observed latent heat and entropy of fusion, 2040 cal. mole^{-1} and 11·41 cal. deg.$^{-1}$ mole^{-1}, are typical of compounds free from both phase transitions and specific heat anomalies below the m. p.; similar behaviour is observed in methyl nitrate.

Thermochemical Properties of Ethyl Nitrate.—(1) *Enthalpy of formation.* Various determinations have been made of the heat of formation of ethyl nitrate. They entail combustion with excess of oxygen, explosion alone, or esterification. The heat of combustion is about 300, of explosion about 80, and of esterification about 5 kcal. mole^{-1}; clearly, although small percentage errors may considerably affect the accuracy of values derived from combustion, explosion is less subject to this, and esterification least of all. All determinations depend, of course, on accurate analyses of reaction products and it is probably analysis errors which limit the accuracy of modern combustion data on such nitrogen compounds. Table 5 lists the values of heat of formation obtained. Some of these refer to the liquid, some to the vapour. The only published value of the heat of vaporization of the liquid available is due to Goodeve (*loc. cit.*) and is based on measurements between −80° C and +20° C. This gives $L_v = 9·2$ kcal. mole^{-1} at 25° C and this value has been used

to correlate the different determinations. It is noteworthy that Berthelot's early determination yields a value closely in agreement with the latest British and American figures, though it is Thomsen's determination which is quoted in standard compilations (*e.g.*,

TABLE 5. *Enthalpy of formation of ethyl nitrate.**

Reference	Thermodynamical quantity determined	Derived enthalpy of formation: liquid	gas
Goodeve [1]	Latent heat of vaporization = 9·2	—	—
Berthelot [2]	Enthalpy of esterification = − 6·2	−46·4	*−37·2*
Thomsen [3]	Enthalpy of combustion of vapour = − 326·4	*−41·7*	−32·5
Kharasch [4]	Correction of Thomsen's combustion data = − 322·4 (theoretical work)	*−45·7*	−36·5
Whittaker, Wheeler, and Pike [5]	Enthalpy of explosion of liquid = − 77·6	−45·7	*−36·5*
This paper	Adopted value	−45·8	−36·6

* Values are in kcal. mole^{-1} at 298° K. Indirect values (derived from Goodeve's values of L_v = 9·2) are in italics.

[1] *Trans. Faraday Soc.*, 1932, **30**, 501. [2] *Ann. Chim. Phys.*, 1880, **20**, 255. [3] "Thermochemische Untersuchungen," Barth, Leipzig (1882–1886). [4] Personal communication (1945). [5] *J. Inst. Fuel*, 1947, **20**, 137.

Bichowsky and Rossini, "Thermochemistry of Chemical Substances," Reinhold Publ. Corp., New York, 1936; Nat. Bur. Standards Circular No. 500, "Chemical Thermodynamical Properties," 1950).

The values adopted are (in kcal. mole^{-1}):

Standard enthalpy of formation of liquid ethyl nitrate $\Delta H_f°(298) = -45·8 \pm 0·8$.
Enthalpy of formation of gaseous ethyl nitrate $\Delta H_f(298) = -36·6 \pm 0·8$.

Berthelot (*loc. cit.*) measured the enthalpy of solution of ethyl nitrate in 180 parts of water as −0·99 kcal. mole^{-1}. Hence the heat of formation of aqueous ethyl nitrate is −46·8 kcal. mole^{-1}. At room temperature, hydrolysis of the ethyl nitrate is much too slow to influence this value.

The value of the standard enthalpy of formation can be combined with the values of the enthalpies of ethyl nitrate and its constituent elements relative to absolute zero determined above to give the value of the molar heat of formation at absolute zero $\Delta H_f(0)$ of ethyl nitrate. The values of $H(298) - H(0)$ kcal. mole^{-1} are: for $C_2H_5{\cdot}NO_3$, 9·240; for $2C_{graphite}$, 0·503; for $2·5H_2$, 5·084; for $1·5O_2$, 3·105; for $0·5N_2$, 1·036; total for elements, 9·73.

$$\text{Hence } \Delta H_f(0)(C_2H_5{\cdot}NO_3) = -45·8 - 9·24 + 9·73 = -45·3 \pm 0·8 \text{ kcal. mole}^{-1}.$$

(2) *Entropy of formation of ethyl nitrate.* The *standard molar entropy of formation* $\Delta S_f°$ may be derived at once from the values of the entropy relative to absolute zero ("absolute entropies") of liquid ethyl nitrate and of its constituent elements in their standard states. The National Bureau of Standards Circular No. 500 lists values of $S_{abs.}°$ in cal. deg.$^{-1}$ mole^{-1} as $2C_{graphite}$, 2·72; $2·5H_2$, 78·03; $0·5N_2$, 22·88; $1·5O_2$, 73·50; total 177·13; and from this work $S_{abs.}°(EtNO_3) = 59·08$. Hence

$$\Delta S_f° = 59·08 - 177·13 = -118·1 \text{ cal. deg.}^{-1} \text{ mole}^{-1}$$

For ethyl nitrate *vapour* at 298° K under its own vapour pressure of 67·5 mm. Hg

$$S_{abs.}(EtNO_3, g) = S_{abs.}° + L_v/T = 59·08 + 9200/298 = 89·95 \text{ cal. deg.}^{-1} \text{ mole}^{-1}$$

For ethyl nitrate *vapour in the (hypothetical) standard state of* 1 atm. pressure at 298° K

$$S_{abs.}°(EtNO_3, g) = 89·95 + \boldsymbol{R} \ln(67·5/760) = 85·14 \text{ cal. deg.}^{-1} \text{ mole}^{-1}$$

The corresponding *entropy of formation*, $\Delta S_f°(EtNO_3, g)$ is −92·68 cal. deg.$^{-1}$ mole^{-1}.

(3) *Free energy of formation of ethyl nitrate.* The values determined for the entropy of formation can be combined with the heat of formation adopted to calculate the free energy of formation of ethyl nitrate. For the *standard state*—liquid nitrate, 298° K, 1 atm.—since $\Delta H_f° = -45·8$ kcal. mole^{-1} and $\Delta S_f° = -118·1$ cal. deg.$^{-1}$ mole^{-1} we have:

$$\Delta F_f°(C_2H_5{\cdot}NO_3, l) = -10·6 \pm 0·8 \text{ kcal. mole}^{-1}.$$

The uncertainty is largely due to the uncertainty in the published values of the heat of formation.

For *gaseous* ethyl nitrate *in the (hypothetical) standard state at* 298° K and 1 atm., the standard molar free energy of formation is similarly obtained. Since $\Delta H_f°(\text{gas}) = -36{\cdot}6$ kcal. mole^{-1} and $\Delta S_f°(\text{gas}) = -92{\cdot}68$ cal. deg.$^{-1}$ mole^{-1} we have : $\Delta F_f°(C_2H_5{\cdot}NO_{3,g}) = -9{\cdot}0$ kcal. mole^{-1}.

The Reaction between Ethyl Alcohol and Nitric Acid.—Ethyl nitrate is prepared by esterification of ethyl alcohol, and it is desirable to know the thermodynamic functions for this reaction. Values may now be derived for the free-energy changes and hence for the equilibrium constant of the reversible reaction between pure components and of the corresponding reaction in aqueous solution.

(1) *Pure liquids.* Inserting the values derived above, and others tabulated, into the equation for esterification, we have, in kcal. mole^{-1}

$$C_2H_5{\cdot}OH + HNO_3 \overset{K}{\rightleftharpoons} C_2H_5{\cdot}NO_3 + H_2O$$

$\Delta H_f°$ values	−66·36	−41·40	−45·8	−68·32	; $\Delta H° = -6{\cdot}36$
$\Delta F_f°$ values	−41·77	−19·10	−10·61	−56·69	; $\Delta F° = -6{\cdot}43$

The free-energy change $\Delta F°$ of $-6{\cdot}4 \pm 0{\cdot}8$ kcal. mole^{-1} corresponds to a thermodynamic equilibrium constant K where $\log_e K = -\Delta F°/\boldsymbol{R}T$, *i.e.*, $K = 5{\cdot}1 \times 10^4$. Thus, with pure reactants at room temperature esterification is greatly favoured, and it is this fact which enabled Berthelot to use this reaction to measure the heat of formation of ethyl nitrate; it proceeds virtually to completion, as he found by precipitating and weighing the ester formed.

(2) *Aqueous solutions.* From the heat of formation of aqueous ethyl nitrate and other tabulated values the thermodynamic properties of the esterification in dilute aqueous solution can be evaluated. Nitric acid in dilute solution is effectively completely ionized.

$$C_2H_5{\cdot}OH_{(aq.)} + H_{(aq.)}^{+} + NO_3^{-}{}_{(aq.)} \overset{K'}{\rightleftharpoons} C_2H_5{\cdot}NO_{3(aq.)} + H_2O$$

$\Delta H_f°$ values...	−68·8	−49·4	−46·8	−68·3	; $\Delta H' = +3{\cdot}1$
$\Delta F_f°$ values...	−43	−26·4	−11	−56·7	; $\Delta F' = +1{\cdot}7$

Esterification is now endothermic ($\Delta H = 3{\cdot}1$ kcal. mole^{-1}) and hydrolysis is favoured in aqueous solutions not only by mass-action effects but by the alteration in the thermodynamic equilibrium constant to $K' = 0{\cdot}058$, almost 10^6 times smaller than its value for pure reactants. Thermodynamics, as usual, tells us nothing about the rates at which these equilibria are attained. Experimentally, it is known that the hydrolysis of ethyl nitrate at room temperature is quite slow and Berthelot's value for its heat of solution is not in error from this source.

We thank Mr. B. W. Rickettson for his assistance. We are also grateful to Professor T. R. C. Fox and Dr. F. P. Bowden, of Cambridge, and to Professor F. E. Simon, of Oxford, for workshop and laboratory facilities.

Department of Chemical Engineering, University of Cambridge.
Clarendon Laboratory, University of Oxford. [*Received, August 12th,* 1953.]

Kinetics of the Depolymerisation of Paraldehyde in Aqueous Solution.

By R. P. Bell and A. H. Brown.

[Reprint Order No. 4667.]

Kinetic measurements are reported on the depolymerisation of paraldehyde at 25° in aqueous solutions of hydrochloric, perchloric, sulphuric, nitric, dichloroacetic, and trichloroacetic acids and of potassium hydrogen sulphate. The reaction is of the first order with respect to paraldehyde, and in solutions of the first four acids the rate depends simply upon the acidity function H_0. Less simple behaviour is shown by solutions of the other three acids, where there appears also to be catalysis by undissociated species. The mechanism of depolymerisation is discussed in terms of these and earlier results.

The depolymerisation of paraldehyde has previously been studied as a homogeneous gas reaction (Coffin, *Canadian J. Res.*, 1932, **7**, 75; Bell and Burnett, *Trans. Faraday Soc.*, 1938, **34**, 420), as an acid-catalysed gas reaction (Bell and Burnett, *ibid.*, 1937, **33**, 555), and as a reaction catalysed by solutions of both proton acids and Lewis acids in non-aqueous solvents (Bell, Lidwell, and Vaughan-Jackson, *J.*, 1936, 1792; Bell and Skinner, *J.*, 1952, 2955). The present paper extends this study to catalysis by aqueous solutions of acids. Measurements of this kind were reported by Skrabal, Stockmair, and Schreiner (*Z. physikal. Chem.*, 1934, *A*, **169**, 177), but were confined to solutions of toluene-*p*-sulphonic acid at a single concentration. Recent work (Walker and Chadwick, *Ind. Eng. Chem.*, 1947, **39**, 974; Paul, *J. Amer. Chem. Soc.*, 1950, **72**, 3813; 1952, **74**, 141) on the depolymerisation of the related substance trioxymethylene (trioxan) in concentrated aqueous acids at 40° indicates that the reaction velocity depends upon the Hammett acidity function of the catalyst solution, but the range of acids and concentrations used was somewhat limited. The present study embraces seven acids over a wide concentration range.

Experimental

Paraldehyde was redistilled (b. p. 121—122°) and used within a few days of distillation. Small amounts of acetaldehyde were formed on storage, but had no effect on the rate of depolymerisation. Older samples also contained traces of acetic acid, but this never exceeded 0·05%, and could thus be neglected in the catalyst solutions used. The acids used were "AnalaR" or pure laboratory reagents, and the concentration of their solutions was related by titration to constant-boiling hydrochloric acid.

All kinetic measurements were carried out at 25° ± 0·01°, and two different methods were used for following the reaction. In the first, the acetaldehyde formed was estimated by the method of Friedemann, Cotonio, and Shaffer (*J. Biol. Chem.*, 1927, **73**, 342). 0·2—0·3 g. of paraldehyde was dissolved in 100 c.c. of catalyst solution, and from time to time 5 c.c. were pipetted into 10 c.c. of M/5-sodium hydrogen sulphite solution. After the solution had stood for 15 min. most of the excess of hydrogen sulphite was removed with N/5-iodine solution, and the removal completed with N/30-iodine (starch indicator). The bisulphite compound was then decomposed by adding about 1 g. of sodium hydrogen carbonate, and the titration completed with N/30-iodine.

Titrations carried out after a long period of time gave titres corresponding to 94—98% depolymerisation. The deficiency is partly due to loss of acetaldehyde by evaporation, and perhaps also to formation of some polymer other than paraldehyde. These effects will only be appreciable in the final stages of the reaction, and we have calculated first-order velocity constants by plotting $\log (x_\infty - x_t)$ against t, where x_t is the observed titre at time t, and x_∞ is the titre for complete reaction calculated from the weight of paraldehyde taken. These plots were linear over at least 70% of the reaction, except in the experiments with nitric acid solutions. With these solutions there was certainly a secondary oxidation of the acetaldehyde formed, and in some instances the observed titres passed through a maximum. The velocity constants recorded for nitric acid solutions are therefore obtained from the first 20—25% of the reaction, and are less accurate than those for the other acids.

The second method used was dilatometric. The depolymerisation of paraldehyde in aqueous solution gives rise to an expansion of about 75 $mm.^3/g.$, compared with about

200 mm.³/g. for the pure liquid or for solutions in non-hydroxylic solvents (Bell, Lidwell, and Vaughan-Jackson, *loc. cit.*). The lower value in aqueous solution is attributable to the hydration of about 60% of the acetaldehyde, with a consequent decrease in volume (Bell and Clunie, *Trans. Faraday Soc.*, 1952, **48**, 439). The volume change is, however, ample for accurate kinetic measurements, and these were carried out in two conventional dilatometers, with capacities of 30 and 50 c.c. and capillaries of cross-sections 0·23 and 0·08 mm.² respectively. The paraldehyde concentration was chosen so as to give a total movement of 10—20 cm. in the capillary. The catalyst solution was de-gassed by suction just before the addition of the paraldehyde and the filling of the dilatometer, and reliable readings could be obtained 5 min. after mixing. First-order velocity constants were obtained graphically by Guggenheim's method (*Phil. Mag.*, 1926, **7**, 538) and no departures from first-order kinetics were detected. The dilatometric method is more convenient and accurate than the analytical one and was therefore employed in the majority of experiments: however, the results recorded later show that there is substantial agreement between the two methods.

There are no recorded data on the acidity functions of solutions of hydrogen sulphates or of dichloroacetic acid, and these were therefore measured by Hammett and Deyrup's indicator method (*J. Amer. Chem. Soc.*, 1932, **54**, 2721), *p*-nitroaniline being used. A visual Klett colorimeter was used, with a blue filter, and in calculating the value of H_0 the pK of the *p*-nitroanilinium ion was taken as 1·11 (Hammett and Paul, *J. Amer. Chem. Soc.*, 1934, **56**, 830). The values obtained are given in Table 1: their accuracy is estimated as $\pm$0·02.

TABLE 1.

k = first-order velocity constant (sec.$^{-1}$). Acid concentrations are in moles/l. of solution.
* denotes that the analytical method was used for determining k.

Hydrochloric acid									
[Acid] ...	0·0217	0·049	0·097	0·145	0·217	0·252	0·388	0·425	0·723
10^5k	0·297	0·545 *	1·19 *	1·85 *	3·30	3·45 *	5·68	6·37 *	15·0
H_0	1·74	1·39	1·05	0·84	0·67	0·56	0·39	0·35	0·10
[Acid] ...	0·969	0·97	1·39	1·58	2·08	2·17	2·36	2·50	3·08
10^5k	19·3	19·8 *	49·0 *	45·0 *	94·5 *	116	136 *	188	280 *
H_0	−0·06	−0·06	−0·30	−0·39	−0·61	−0·64	−0·70	−0·76	−0·95
Perchloric acid									
[Acid] ...	0·101	0·202	0·505	0·92	1·01	1·01	1·33	1·52	1·67	2·02	2·41
10^5k	1·63	2·98	9·75	22·2 *	31·5	24·3 *	60·2	70·2	89·8	138 *	208
H_0	1·00	0·69	0·23	−0·05	−0·13	−0·13	−0·38	−0·48	−0·55	−0·70	−0·86
Sulphuric acid									
[Acid] ...	0·352	0·528	0·703	1·06	1·58	2·11			
10^5k	6·08	8·80	16·3	30·0	74·0	158			
H_0	0·40	0·22	0·09	−0·16	−0·48	−0·78			
Nitric acid									
[Acid] ...	0·186	0·372	0·558	0·744	0·930				
10^5k	3·07 *	6·30 *	14·0 *	19·7 *	31·3 *				
H_0	0·78	0·43	0·19	0·02	−0·07				
Trichloroacetic acid									
[Acid] ...	0·294	0·490	0·980	1·95	1·96	2·44	3·42	5·58	
10^5k	3·17	5·20 *	9·55 *	15·6	15·0 *	22·7	34·5	97·3	
H_0	0·72	0·66	0·62	0·58	0·58	0·58	0·58	0·58	
Dichloroacetic acid									
[Acid] ...	0·535	0·780	1·17	2·34	4·68				
10^5k	2·47	2·72	3·17	3·17	7·75				
H_0	1·13	1·01	0·91	0·82	0·82				
Potassium hydrogen sulphate									
[Acid] ...	0·241	0·510	1·02	1·33	1·52	1·70	2·04	2·28	2·66
10^5k	1·31	2·67	6·07	9·38	10·7	13·3	16·8	21·7	29·2
H_0	1·04	0·75	0·58	0·57	0·56	0·56	0·55	0·54	0·54

Results.—The results of the kinetic measurements are given in Table 1. The acidity functions (H_0) given for hydrochloric, nitric, and trichloroacetic acids are taken from the work of Hammett and Paul (*loc. cit.*). Those for perchloric and sulphuric acid are from Hammett and Deyrup's measurements (*loc. cit.*), with allowance for the revision of the acidity scale made by Hammett and Paul. The concentrations recorded by these authors are in moles/1000 g. of solvent or in weight %: they have been converted to moles/l. by using the densities of the

solutions, and the values in the table obtained by graphical interpolation. The acidity functions for potassium hydrogen sulphate and dichloroacetic acid solutions are from our own measurements.

Discussion

We shall consider first those acids which are substantially completely dissociated in the concentration range considered, *i.e.*, hydrochloric, perchloric, nitric, and sulphuric (first dissociation). In dilute solutions the reaction velocity is directly proportional to acid concentration, and independent of which acid is being used. The value given by Skrabal *et al.* (*loc. cit.*), $k = 0{\cdot}68 \times 10^{-5}$ sec.$^{-1}$ in 0·05M-toluene-*p*-sulphonic acid, is also

Fig. 1.

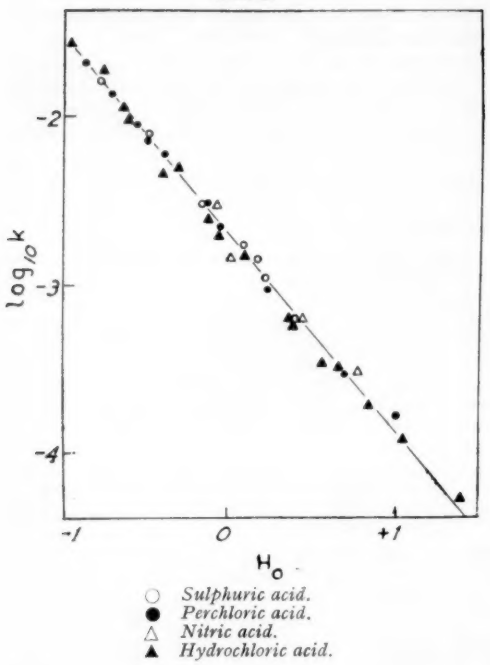
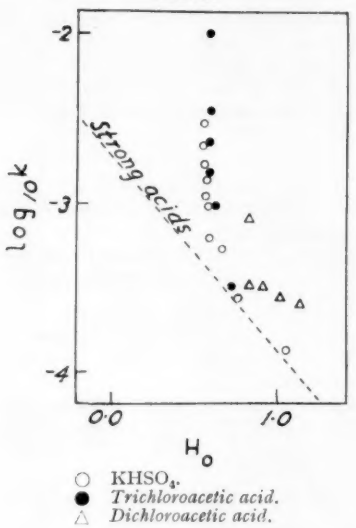


Fig. 2.



concordant with ours. In more concentrated solutions the reaction velocity increases more rapidly than the concentration, and is in fact roughly proportional to the square of the concentration above about 0·5M. Over the whole concentration range the reaction velocity runs closely parallel with the Hammett acidity function. This is illustrated in Fig. 1, which shows a plot of $\log_{10} k$ against H_0 for the four strong acids. There is some tendency for the plot to curve upwards at higher concentrations, and the straight line in the figure has a slope a little greater than unity (1·16) : however, these deviations are much more marked if $\log_{10}$ [acid] is plotted in place of H_0.

The remaining acids (trichloroacetic, dichloroacetic, and the hydrogen sulphate ion) are incompletely dissociated at the concentrations employed, and for these solutions there is no parallelism with the acidity function. Fig. 2 shows a plot of $\log_{10} k$ against H_0, the broken line representing the relation found for the four strong acids. The velocity is in each case considerably greater than would be expected from the acidity function, as was also found in the inversion of sucrose by solutions of trichloroacetic acid (Hammett and Paul, *loc. cit.*). This behaviour suggests that in these solutions there is catalysis not only by hydrogen ions, but also by other acidic species; or, expressed in other words, that the transition state of the reaction can associate specifically with the anions $CCl_3{\cdot}CO_2^-$,

$CHCl_2{\cdot}CO_2^-$, and $SO_4^=$ in a manner not paralleled by the cation produced in the indicator measurements of H_0.

There is no reliable information about the degree of dissociation of the concentrated solutions of di- and tri-chloroacetic acid used, but an estimate can be made for the hydrogen sulphate solutions. Young and Blatz (*Chem. Reviews*, 1949, **44**, 98) have re-interpreted Rao's measurements (*Indian J. Phys.*, 1940, **14**, 143) on the Raman effect in 3—10M-sulphuric acid, and deduce values for the concentration dissociation constant of HSO_4^- (K'_2) in this range. Davies, Jones, and Monk (*Trans. Faraday Soc.*, 1952, **48**, 921) have critically considered various measurements on solutions of sulphuric acid and hydrogen sulphates, and give a table of K'_2 for sulphuric acid solutions up to 0·05M. By combining these two sets of results we can interpolate roughly the value of K'_2 for intermediate concentrations, and if it is assumed that K'_2 has the same value in solutions of H_2SO_4 and $KHSO_4$ of the same concentration it is possible to calculate the composition of the $KHSO_4$ solutions used in the present work. The results obtained are given in the first three columns of Table 2: they are approximate only, but show clearly that the reaction velocity increases much more rapidly than the hydrogen-ion concentration.

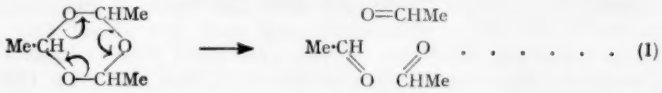
TABLE 2. *Catalysis by hydrogen sulphate solutions.*

$[KHSO_4]$	$[HSO_4^-]$	$[H^+]$	10^5k	$10^5k(H^+)$	$10^5\{k - k(H^+)\}/[HSO_4^-]^2$
0·241	0·153	0·088	1·31	1·1	(14)
0·510	0·360	0·150	2·67	2·0	5·2
1·02	0·77	0·25	6·07	3·3	4·7
1·33	1·03	0·30	9·38	4·2	4·9
1·52	1·19	0·33	10·7	4·7	4·2
1·70	1·33	0·37	13·3	5·2	4·6
2·04	1·61	0·43	16·8	6·7	3·9
2·28	1·79	0·47	21·7	7·3	4·5
2·66	2·11	0·55	29·2	8·8	4·6

We can make an approximate allowance for catalysis by hydrogen ions by subtracting the velocity observed in a hydrochloric solution of concentration equal to $[H^+]$: these velocities are shown as $k(H^+)$ in col. 5 of Table 2. The constancy of the ratio given in the last column of the table shows that the remaining velocity is closely proportional to $[HSO_4^-]^2$. This conclusion cannot claim much quantitative weight, but there seems no doubt that the concentration of hydrogen sulphate ion enters the kinetic expression to a power greater than unity. It is likely that the same is true for catalysis by undissociated di- and tri-chloroacetic acids, though reliable data are lacking on the degree of dissociation of their aqueous solutions: an apparent kinetic order greater than unity (1·5—2·5) is also found when the depolymerisation of paraldehyde is catalysed by solutions of proton acids or of Lewis acids in non-dissociating solvents (Bell, Burnett, and Vaughan-Jackson, *loc. cit.*; Bell and Skinner, *loc. cit.*). Quite apart from any kinetic considerations, it is strange that the acidity functions of all three acids (dichloroacetic, trichloroacetic, and potassium hydrogen sulphate) should become almost independent of concentration in their more concentrated solutions, in spite of considerable variations in hydrogen-ion concentration. We cannot suggest any explanation for this behaviour.

We shall now consider the bearing of these results on the mechanism of depolymerisation. The proportionality between $-\log_{10}k$ and H_0 for the four strong acids suggests that the transition state is formed by the simple addition of a proton to a paraldehyde molecule, without the intervention of a water molecule (Hammett and Deyrup; Hammett and Paul, *locc. cit.*). The same conclusion had already been reached by Paul (*loc. cit.*) for the analogous depolymerisation of trioxymethylene, though on less complete evidence. As mentioned on p. 774, the depolymerisation of paraldehyde takes place readily under a variety of conditions in the absence of water or any similar molecule: for example, as a gas reaction (catalysed and uncatalysed) and in solutions of either proton acids or electron-acceptor molecules in aprotic solvents. This suggests that even in aqueous solution the water molecule is not concerned in any stage of the reaction: this contrasts with the view of Skrabal, Stockmair, and Schreiner (*loc. cit.*), who regard the reaction as analogous to the hydrolysis of acetals and ethers, taking place through the intermediate semiacetal HO·CHMe·O·CHMe·O·CHMe·OH. However, it should be noted that cyclic trimeric

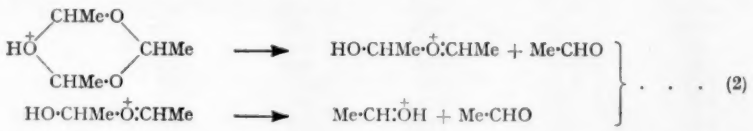
aldehydes such as paraldehyde differ structurally from other ethers and acetals in that they can break down by a simple electronic re-arrangement, *e.g.*,



(1)

and it therefore seems natural to assume that this type of mechanism operates both in the presence and in the absence ot water.

If the non-hydrolytic mechanism is accepted, we must explain the part played by the acid catalyst. Since the change represented in (1) involves the passage of electrons from one side of the oxygen atom to the other, it may be supposed that the presence of a positive charge on the oxygen (produced by a proton or other acceptor molecule) will facilitate this change. An alternative view is as follows. In the absence of a catalyst the removal of a single acetaldehyde molecule from the paraldehyde ring would leave behind an unstable species (either a di-radical or the ion $\bar{O}\cdot CHMe\cdot O\cdot\overset{+}{C}HMe$), and it is more probable that depolymerisation takes place in a single step. In the catalysed reaction, on the other hand, it is easy to picture successive steps such as



(2)

and the function of the catalyst may be to enable the reaction to take place in stages.

The kinetic orders of reaction reported in this and earlier papers suggest strongly that depolymerisation can be effected by the attachment of a single hydrogen ion to the paraldehyde molecule, while in catalysis by uncharged acids and by HSO_4^- the simultaneous action of two catalyst molecules is much more effective. This behaviour is reasonably accounted for by the fact that the ring has to be broken in two places in order to complete depolymerisation. In catalysis by hydrogen ions simultaneous attachment to two oxygens will be hindered by the mutual repulsion of the positive charges, and a stepwise mechanism such as (2) is more feasible, while with the other types of catalyst the proximity of an anion (*e.g.*, $R\cdot CO_2^-$, $SO_4^=$) will partly neutralise the repulsion between the positive charges.

There is, however, some ambiguity in assigning a kinetic order to this reaction. The results for aqueous solutions of strong acids could be represented in the form $k = k_1[\text{acid}] + k_2[\text{acid}]^2$, the second term dominating at higher concentrations, though we have preferred here to interpret them in terms of a reaction depending upon the first power of the acidity function.* Conversely, the high catalytic orders assigned to solutions of carboxylic acids in non-aqueous solvents (Bell, Lidwell, and Vaughan-Jackson, *loc. cit.*) might disappear if the results were interpreted in terms of acidity functions. No data are available on the acidities of such solutions, though some indicator and e.m.f. measurements suggest that in hydrocarbon solvents the acidity increases more rapidly than the concentration (La Mer and Downes, *J. Amer. Chem. Soc.*, 1931, **53**, 888; Griffiths, *J.*, 1938, 818). However, the following facts are unaffected by these uncertainties: (*a*) in dilute aqueous solutions of strong acids the reaction velocity is proportional to the first power of the catalyst concentration, and (*b*) in dilute solutions of hydrogen chloride and of Lewis acids in non-dissociating solvents the reaction velocity is proportional to the square of the catalyst concentration. These facts demand an explanation of the type given in the last paragraph.

PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, September 22nd*, 1953.]

* The fact that the line in Fig. 1 has a slope slightly greater than unity may indicate a small contribution proportional to the square of the acidity function.

Alkyl–Oxygen Fission in Carboxylic Esters. Part XIII. The Resolution and Reactions of* 1 : 2 : 2 : 2-*Tetraphenylethanol. Crystalline Solvent Complexes of* (+)-1 : 2 : 2 : 2-*Tetraphenylethyl Hydrogen Phthalate.*

By L. Ellison and J. Kenyon.

[Reprint Order No. 4827.]

By the usual procedure (±)-1 : 2 : 2 : 2-tetraphenylethanol can be converted into its (+)- and (−)-hydrogen phthalic esters, which by interaction with lithium aluminium hydride yield the (+)- and the (−)-ethanol, respectively.

The hydrogen phthalate reacts, somewhat slowly, with alkali to yield, not the original ethanol, but its decomposition products triphenylmethane and benzaldehyde: under acid conditions the principal product is tetraphenylethylene. The optically active forms of the hydrogen phthalate readily yield stable crystalline complexes containing one molecule of solvent. In marked contrast the (±)-hydrogen phthalate exhibits no such tendency to complex-formation.

As part of our study of the hydrolysis of carboxylic esters we have examined the behaviour of 1 : 2 : 2 : 2-tetraphenylethyl hydrogen phthalate. This ester is formed in excellent yield by combination of the alcohol with phthalic anhydride at 100° in the presence of pyridine: by fractional crystallisation of its brucine salt it is separated, easily and almost quantitatively, into its (+)- and (−)-isomerides. This separation is greatly facilitated by the marked difference in solubility of the (+)- and (±)-isomerides. Rotatory powers are given in Table 1.

A solution of the hydrogen phthalate in aqueous alcoholic sodium hydroxide (2·5 mols.) remains unchanged for many weeks at room temperature but when heated on the steam-bath for several hours it slowly undergoes decomposition according to the equation

$$NaO_2C\cdot C_6H_4\cdot CO_2\cdot CHPh\cdot CPh_3 + NaOH \longrightarrow C_6H_4(CO_2Na)_2 + CHPh_3 + PhCHO$$

and no trace of the original alcohol can be detected.

Table 1. *Specific rotatory powers of* (+)-1 : 2 : 2 : 2-*tetraphenylethyl hydrogen phthalate in various solvents at* 18° (*c*, 1·500; *l*, 1).

Solvent	6439 Å	5893 Å	5790 Å	5461 Å	5086 Å	4800 Å	4358 Å
Acetone	+86·1°	+107°	+114°	+137°	+155°	+180°	+245°
Ethanol	82·6	103	107	115	130	147	221
Ethylbenzene	61·7	65	75	85	94	101	117

No variation of $[\alpha]_{5893}$ was observed when *c*, in acetone solution, was increased from 0·4 to 2·7: the values of $[\alpha]_{5893}$ in solvents other than acetone are independent of whether the solutions are made with the unsolvated ester or with its acetone complex provided that *c* is calculated on the basis of unsolvated ester (see below). Replacement of sodium hydroxide by sodium carbonate resulted in no reaction: even after 50 hours' heating the hydrogen phthalate was recovered unchanged.

In view of these results 1 : 2 : 2 : 2-tetraphenylethanol was heated under reflux with aqueous alcoholic sodium hydroxide: after 5 min. the solution yielded triphenylmethane and benzaldehyde, each isolated in 65% yield. This decomposition was observed by Delacre (*Bull. Acad. roy. Belg.*, 1890, **20**, 109), and it has now been shown to occur under conditions favourable to ester hydrolysis. The reaction is rapid in alcoholic solution and its rate is not appreciably affected by dilution with water but is dependent upon alkali concentration. Similar decomposition occurs in dry benzene solution at room temperature in presence of sodium ethoxide.

* Part XII, *J.*, 1953, 3619.

Thus it seems likely that the formation of triphenylmethane and benzaldehyde during reactions of 1 : 2 : 2 : 2-tetraphenylethanol and its hydrogen phthalate is dependent on the release of the anion $Ph_3C{\cdot}CHPh{\cdot}O^-$ which results from acyl–oxygen fission. The sodium salt of the hydrogen phthalate in aqueous solution when mixed with sodium toluene-*p*-sulphinate remained unchanged during 6 months—the non-formation of sulphone confirms that esters of this alcohol show little or no tendency to react by alkyl–oxygen fission under alkaline conditions. When conditions are such that the alkoxide anion is not released then the group remains intact, *e.g.*, the esterification of the ethanol with phthalic anhydride in the presence of pyridine results in no significant side-reaction; furthermore the product of interaction of the alcohol with ethylmagnesium iodide—during which the calculated amount of ethane is evolved—regenerates the unchanged alcohol on decomposition with water.

It therefore seems highly probable that the hydrolysis of 1 : 2 : 2 : 2-tetraphenylethyl hydrogen phthalate by aqueous alkali occurs by acyl–oxygen fission.

Since alkaline hydrolysis failed to yield the ethanol from its hydrogen phthalate, hydrolysis by acid was tried and here again the reaction proved abnormal, the product being tetraphenylethylene. It was shown by Skell and Hauser (*J. Amer. Chem. Soc.*, 1942, **64**, 2633) that this ethanol in benzene solution with dry hydrogen bromide gives high yields of tetraphenylethylene. It is thus probable that acid hydrolysis of 1 : 2 : 2 : 2-tetraphenylethyl hydrogen phthalate involves alkyl–oxygen fission.

On the other hand when a solution of the hydrogen phthalate in formic acid containing an equivalent amount of sodium toluene-*p*-sulphinate was heated for a few minutes no sulphone was formed, the main product being again tetraphenylethylene. It is thus possible that no carbonium ion exists long enough to react with an anion of such high co-ordinating power as the sulphinate ion : this result supports the suggestion by Skell and Hauser (*loc. cit.*) that rearrangement is simultaneous with fission of the alkyl–oxygen bond:

$$R{\cdot}CO{\cdot}O{\cdot}CHPh{\cdot}CPh_3 \longrightarrow R{\cdot}CO{\cdot}\bar{O} + \overset{+}{C}HPh{\cdot}CPh_3 \xrightarrow[\text{rapid}]{\text{very}} Ph_2C{=}CPh_2 + \overset{+}{H}$$

Reaction of (+)-1 : 2 : 2 : 2-*Tetraphenylethyl Hydrogen Phthalate with Lithium Aluminium Hydride.*—The isolation of an optically active tertiary alcohol from its hydrogen phthalate by means of lithium aluminium hydride has been described by Doering and Zeiss (*J. Amer. Chem. Soc.*, 1950, **72**, 147), and this reaction has now been applied in parallel manner to (+)- and (−)-1 : 2 : 2 : 2-tetraphenylethyl hydrogen phthalate. Rotatory powers are in Table 2.

TABLE 2. *Specific rotatory powers of* (−)-1 : 2 : 2 : 2-*tetraphenylethanol in various solvents at* 20° (*c*, 1·300; *l*, 1).

Solvent	6439 Å	5893 Å	5780 Å	5461 Å	5086 Å	4800 Å	4358 Å
Acetone	−59·0°	−69·5°	−72·0°	−81·0°	−96·0°	−116°	−146°
Ethanol	59·5	61·9	76·5	86·7	105	126	154
Benzene	84·2	105	119	143	168	209	252

Retention of full optical activity by the liberated ethanols (proved by reconversion into hydrogen phthalates possessing their original rotatory powers) indicates clearly that cleavage of the esters has occurred at the acyl–oxygen bond exclusively.

Molecular Compounds of Optically Active 1 : 2 : 2 : 2-*Tetraphenylethyl Hydrogen Phthalate.*—A most interesting development of this investigation has been the isolation of a series of compounds in which the optically active forms of 1 : 2 : 2 : 2-tetraphenylethyl hydrogen phthalate occur in combination with a molecular proportion of a solvent.

A solution of the (+)- or (−)-form of the hydrogen phthalate in a solvent, other than a paraffin hydrocarbon, deposits crystals of the hydrogen phthalate which contain, in most cases, 1 mol. of the solvent, *e.g.*, acetone, thus rendering it tedious to obtain a solvent-free compound. The most convenient method of doing this is to heat the hydrogen phthalate–acetone complex in a current of air until it has lost weight corresponding to 1 mol. of

acetone and acquired a m. p. 181—182° : this material separates from (much) light petroleum in needles, m. p. 183°.

The various crystalline complexes were kept at 95—100° for some 20 min. to remove adhering solvent and then titrated with standard alkali; the equivalent weight corresponded to 498 + *M* where *M* is the molecular weight of the solvent—results are given in Table 3.

Possibly the most significant behaviour of these compounds is the following. When acetone solutions of the (+)- and the (−)-hydrogen phthalate, each of which separately

TABLE 3.

Solvent	Crystalline form	M. p.	Equiv. Found	Equiv. Calc.*
Acetone	Needles	118—122°	558	556
Ethyl ether	,,	110—112	570	572
Ethyl *n*-propyl ether	,,	87—89	580	586 †
n-Butyl ether	Prisms	136—140	550	630
Benzene	,,	140—145	574	576
Toluene	Plates	110—112	556	590
Ethylbenzene	Needles	106—108	560	604 ‡
Nitrobenzene	Hexagonal plates	110—112	625	621
Methanol	Prismatic needles	126—128	532	530
Ethanol	Needles	135—140	540	544
tert.-Butanol	Prisms	145—148	565	572
Chloroform	Prismatic needles	116—120	600	620
Carbon tetrachloride	,, ,,	181—183	530	652
Acetic acid	,, ,,	114—116	330	279 §
Carbon disulphide	Needles	132—137	518	574 ‖

* For 1 : 1-complex.

† Owing to its low m. p. this compound was dried in a vacuum desiccator at room temp.

‡ This expt. was repeated with slight modifications as follows : the crystalline complex which separated from ethylbenzene–light petroleum was placed in a stream of air at room temp. for 10 min. : it then had m. p. 100—102° (decomp.) and equiv. 590. After heating at 95° for 10, 30, and 60 min. the equiv. was 567, 540, and 520, respectively. The final product sintered at 108° and melted at 179—180°.

§ This compound separates from the acetic acid solution on addition of water : the equivalent corresponds to hydrogen phthalate : solvent ratio of 3 : 2.

‖ Best prepared by the addition of much light petroleum to a warm dilute solution in carbon disulphide. More concentrated solutions set to a granular gel.

would deposit needles, m. p. 118—122°, of the solvated compound, are mixed, the large flat prisms, m. p. 219°, of the (±)-hydrogen phthalate which separate contain no solvent of crystallisation.

The pronounced readiness of the (+)- or (−)-hydrogen phthalate to combine with acetone is illustrated by the following : From concentrated solutions in dry ethanol the hydrogen phthalate separated in needles containing one equivalent of the solvent but from aqueous ethanolic solutions no definitely crystalline material could be separated. However, when acetone was added to these aqueous alcoholic solutions the crystalline hydrogen phthalate readily separated as the acetone complex.

EXPERIMENTAL

Benzopinacol was prepared in very good yield by the method (i) given in *Org. Synth.* Coll. Vol. II, p. 71, or (ii) of Gomberg and Bachmann (*J. Amer. Chem. Soc.*, 1927, **49**, 241) and converted into β-benzopinacolone, also in good yield, by Gomberg and Bachmann's method (*loc. cit.*).

1 : 2 : 2 : 2-Tetraphenylethanol was prepared from β-benzopinacolone most conveniently by Levy and Lagrave's method (*Bull. Soc. chim.*, 1928, **43**, 440) with the modification of adding the pinacolone, not intermittently as a solid, but continuously as an ethereal suspension. It separates from ethanol in prisms, m. p. 152°.

(±)-1 : 2 : 2 : 2-*Tetraphenylethyl Hydrogen Phthalate.*—A mixture of the ethanol (20 g.), phthalic anhydride (11·5 g.), and pyridine (15 c.c.) was heated on the steam-bath for 8 hr. Next day the resultant solid was dissolved in hot acetone (1500 c.c.), and the cooled and stirred

solution acidified with hydrochloric acid and slowly diluted with water. The resulting fine crystalline *product* (24 g.) separated from *n*-butyl acetate (250 c.c.) in prisms, m. p. 221—223° (decomp.) [Found, by titration with $Ba(OH)_2$: *M*, 500. $C_{23}H_{27}O_4$ requires *M*, 498].

(+)-1 : 2 : 2 : 2-*Tetraphenylethyl Hydrogen Phthalate.*—A solution of the (±)-hydrogen phthalate (50 g.) and brucine (40 g.) in hot acetone (1300 c.c.), after cooling, deposited the brucine salt (70 g.), m. p. 162—167°; after digeston with boiling methyl acetate (1200 c.c.) this salt (35 g.) had m. p. 162—164° and was almost optically pure brucine salt of (+)-1 : 2 : 2 : 2-tetraphenylethyl hydrogen phthalate (*A*) (see below). This salt's being but sparingly soluble in suitable solvents renders fractional crystallisation a laborious and wasteful process. On the other hand there is a wide difference in solubility—as well as in melting point—between the (±)- and the (+)- or (−)-hydrogen phthalates, thus making the separation of the optically pure compound from admixed racemic material a simple and efficient procedure. Accordingly a combination of the two procedures was adopted similar to that used for the resolution of 1-phenylethanol by Downer and Kenyon (*J.*, 1939, 1156); brief details are as follows.

The brucine salt (35 g.), suspended in cold acetone (200 c.c.), was acidified (dropwise; stirring) with hydrochloric acid: water was then added to dissolve the precipitated brucine hydrochloride. The solution soon deposited the hydrogen phthalate, small needles, m. p. *ca.* 120° (decomp.): this, by crystallisation from acetone–light petroleum yielded optically pure (+)-1 : 2 : 2 : 2-*tetraphenylethyl hydrogen phthalate* (14·8 g.), as needles, m. p. 118—122° (decomp.) [Found: *M* (by titration), 557. $C_{34}H_{28}O_4,Me_2CO$ requires *M*, 556].

The filtrate, after addition of a few drops of water, yielded optically impure (+)-hydrogen phthalate (4 g.), m. p. 195° (decomp.). A further crop of the brucine salt, by similar treatment, yielded optically pure (+)-hydrogen phthalate (5·4 g.).

(−)-1 : 2 : 2 : 2-*Tetraphenylethyl Hydrogen Phthalate.*—The more soluble fractions of the brucine salt, by similar treatment, yielded optically pure (−)-1 : 2 : 2 : 2-*tetraphenylethyl hydrogen phthalate*, needles (22·1 g.), m. p. 118—122° (decomp.) (Found: *M*, 555). The combined yield of optically pure (+)- and (−)- hydrogen phthalate was 42·3 g. (this includes about 10% of combined acetone) = 76%: some 7 g. of largely (±)-hydrogen phthalate were recovered.

(+)- *and* (−)-1 : 2 : 2 : 2-*Tetraphenylethanol.*—The (+)-hydrogen ester (2 g.) was introduced, by extraction from a Soxhlet apparatus, into a flask containing anhydrous ether (100 c.c.) and lithium aluminium hydride (0·8 g.): the extraction was complete after 9 hr., and the heating was continued for a further 3 hr. Working up in the usual way yielded (+)-1 : 2 : 2 : 2-tetraphenylethanol, which separated from light petroleum in prisms (1·0 g.), m. p. 120—121°, $[\alpha]_D$ +61·0° (*c*, 1·00 in acetone; *l*, 1).

Similarly the (−)-hydrogen ester yielded (−)-1 : 2 : 2 : 2-tetraphenylethanol as prisms (1·2 g.), m. p. 120—121°, $[\alpha]_D$ −60·0° (*c*, 0·900 in acetone; *l*, 1).

A mixture of equal amounts of the (+)- and the (−)-ethanol had m. p. 149—151°, alone and when mixed with (±)-1 : 2 : 2 : 2-tetraphenylethanol, m. p. 152°.

A mixture of the (−)-ethanol (0·1 g.), phthalic anhydride (0·05 g.), and pyridine (1 c.c.) when heated for 10 hr. yielded the (−)-hydrogen phthalate (as its acetone complex), needles, m. p. 118—122° (decomp.) alone and mixed with an authentic specimen.

In a similar manner, but with avoidance of acetone, the (+)-ethanol yielded the (+)-hydrogen phthalate, which, without crystallisation, had m. p. 170—171°, $[\alpha]_D$ +102° (*c*, 0·800 in acetone; *l*, 1).

Reactions of (−)-1 : 2 : 2 : 2-*Tetraphenylethyl Hydrogen Phthalate.*—(i) *With sodium hydroxide.* A solution of the (−)-acid ester (1 g.) in 0·2N-alcoholic sodium hydroxide (25 c.c.; 2·5 mol.) was heated on the steam-bath. After 2 hr. sodium phthalate (0·3 g.) had separated, and dilution of the filtrate with water yielded triphenylmethane (0·33 g.; m. p. and mixed m. p. 94°). Addition of 2 : 4-dinitrophenylhydrazine to the filtrate yielded benzaldehyde 2 : 4-dinitrophenylhydrazone (0·4 g.; m. p. and mixed m. p. 237°). From the filtrate there was isolated unchanged (−)-hydrogen phthalate (as its acetone complex) (0·2 g.; m. p. 110°). These quantities represent yields of over 80%. This reaction occurs at room temp. but much more slowly. The (+)-acid ester was recovered after being heated for 50 hr. with (*a*) aqueous sodium carbonate or (*b*) in acetone (20 c.c.) containing hydrochloric acid (0·1N; 10 c.c.).

(ii) *With ethanolic hydrochloric acid.* A solution of the (−)-acid ester (0·5 g.) in ethanol (15 c.c.) containing hydrochloric acid (0·2 c.c.) was heated under reflux for 6 hr. and then diluted with water. The precipitated crystalline material was separated by fractional crystallisation from ethanol into (*a*) unchanged (−)-acid ester (0·25 g.), (*b*) tetraphenylethylene (0·02 g.), m. p. 221—223° (alone and mixed with an authentic specimen, and (*c*) the neutral ester—*ethyl*

1 : 2 : 2 : 2-*tetraphenylethyl phthalate* (0·06 g.), irregular prisms, m. p. 178—179°, $[\alpha]_D$ −136° (*c*, 0·800 : *l*, in acetone) (Found : C, 81·7; H, 5·8. $C_{36}H_{30}O_4$ requires C, 82·3; H, 5·5%).

This neutral ester was also prepared from the (−)-acid ester by (*a*) the action of cold ethanolic hydrogen chloride and (*b*) the action of ethyl iodide on the potassium salt. Both products had m. p. 178—179°, alone or mixed with the original specimen, the structure of which is thus confirmed.

The corresponding ethyl ester of the (+)-hydrogen phthalate had m. p. 178—179°; a mixture with the corresponding (−)-ethyl ester had m. p. 160—162°.

(iii) *With methyl(or ethyl)magnesium iodide.* Even after being heated under reflux for 3 hr. with Grignard reagent (6 mol.) the (−)-acid ester was largely recovered together with some tetraphenylethylene (5—20%).

(iv) *With formic acid.* A solution of the (+)-acid ester (0·1 g.) in formic acid (90%; 4 c.c.) after 2 hr. on the steam-bath yielded tetraphenylethylene (0·06 g.), m. p. 223—225° alone and mixed with an authentic specimen. When heated with glacial acetic acid at 100° for 8 hr. the acid ester was unchanged : hot aqueous acetic acid (50%), however, slowly effects the decomposition.

Non-formation of p-*Tolyl Sulphone.*—A solution of the (+)-hydrogen phthalate (0·5 g.) in ethanol (5 c.c.), neutralised with sodium hydroxide, was mixed with a solution of sodium toluene-*p*-sulphinate (0·5 g.) in water (10 c.c.). After 6 months the solution yielded unchanged (+)-hydrogen phthalate (0·4 g.), m. p. and mixed m. p. 118—120°.

When a solution of the two components in formic acid was heated on the steam-bath for 30 min. the main product was tetraphenylethylene. No trace of sulphone was observed in either experiment.

Reactions of 1 : 2 : 2 : 2-*Tetraphenylethanol.*—(i) *With sodium hydroxide.* A solution of the tetraphenylethanol (1 g.) in ethyl alcohol (20 c.c.) containing sodium hydroxide (50%; 1 c.c.) was heated under reflux for 5 min. and yielded triphenylmethane (0·45 g.) and benzaldehyde (as its 2 : 4-dinitrophenylhydrazone; 0·58 g.). A similar solution, after 10 days at room temperature, gave the same products in 30% yield.

(ii) *With alcoholic hydrochloric acid.* A solution of the tetraphenylethanol (0·5 g.) in ethyl alcohol (10 c.c.) containing hydrochloric acid (0·6 c.c.) when heated under reflux for 6 hr. yielded tetraphenylethylene (0·1 g.) and the unchanged ethanol (0·3 g.).

(iii) *With methylmagnesium iodide (in anisole solution).* When the tetraphenylethanol was treated with Grignard reagent, methane (20 c.c. : calc. 21 c.c.) was liberated; the resulting magnesium complex, after being mixed with acid, yielded the original ethanol quantitatively.

(iv) *The action of heat.* The ethanol (1 g.) when heated at 200—210° for 5 min. yielded triphenylmethane (0·5 g.), and benzaldehyde (as its 2 : 4-dinitrophenylhydrazone; 0·75 g.) in 95% yield. At 180° no decomposition occurred during 5 min.

(v) *With sodium ethoxide in benzene solution.* A mixture of benzene (20 c.c.), absolute ethanol (1 c.c.), and sodium (excess) was heated under reflux, and the solution filtered into a solution of the ethanol (1 g.) in benzene (10 c.c.). Next morning the solution yielded benzaldehyde (as its dinitrophenylhydrazone) and triphenylmethane (0·5 g.), m. p. 92—93° (alone and mixed); the yield was 72%.

Solvent Complexes of (+)- *and* (−)-1 : 2 : 2 : 2-*Tetraphenylethyl Hydrogen Phthalate.*—During investigation of the resolution of the (±)-hydrogen phthalate an unusual property of the optically active forms of this compound was encountered, namely the readiness with which they combine with solvents. The solvent molecules appear to be, in some cases at least, firmly bound in the crystal structure as is shown by the following results.

(i) The (+)-hydrogen phthalate, obtained by decomposition with acid of the less soluble brucine salt, separates from acetone–light petroleum in needles, m. p. 118—122° (decomp.) [Found, by titration of its acetone solution with aqueous baryta : equiv., 558. Calc. for the pure (unsolvated) ester : equiv., 498].

These crystals, when heated at 95° for 1 hr. suffered neither loss in weight nor alteration of m. p. : after being heated at 90—100°/20 mm. for 5 hr. they had lost 7% in weight but the m. p. was unchanged : after a short period at 108—110°/20 mm. no melting occurred but there was an additional loss in weight of 4%. The crystals now had m. p. 180—181°, $[\alpha]_D$ +103° (in acetone), equiv., 490.

(ii) The (−)-hydrogen phthalate [needles from acetone–light petroleum, m. p. 118—122° (decomp.), 14·8 g.] was heated at 95°/20 mm. but suffered no loss in weight during 2 hr. It was then reheated under the same pressure with a slow stream of air passing over it and through an acidified solution of 2 : 4-dinitrophenylhydrazine. No reaction was visible in

the hydrazine solution until the bath-temperature reached 109°, then a heavy yellow precipitate separated rapidly. This precipitate, after recrystallisation, formed needles, m. p. 125—126°, alone or mixed with authentic acetone 2 : 4-dinitrophenylhydrazone.

After 4 hr. the hydrogen phthalate had lost 1 mol. of acetone; the m. p. had risen to 182—188°, and the equivalent fallen to 499; $[\alpha]_D$ +107° (*c*, 2·160 in acetone; *l*, 1).

When these solvent-free crystals were finely powdered and mixed with acetone hard masses were formed, reminiscent of the behaviour of anhydrous sodium carbonate on addition of water; the solid dissolved when heated and the resulting solution, after addition of light petroleum, yielded the crystalline ester, m. p. 118—122° (decomp.) (Found: equiv., 554. Calc. for $C_{34}H_{26}O_4,COMe_2$: equiv. 556).

The corresponding (+)-hydrogen phthalate behaved similarly.

When the solvent-free (+)-hydrogen phthalate (0·5 g.; m. p. 182—183°) was added to cold benzene (2 c.c.) a clear solution resulted; this, within 1 min., deposited small prisms (0·5 g.), m. p. 140—145° (decomp.) (see Table 3), of a benzene complex (0·5 g.), which dissolved readily in cold acetone (2 c.c.): the solution, on being scratched, deposited the (+)-hydrogen phthalate–acetone complex as needles, m. p. 118—122° (decomp.).

Crystallisation of (−)-1 : 2 : 2 : 2-*Tetraphenylethyl Hydrogen Phthalate in a Solvent-free Condition.*—A solution of the (−)-hydrogen phthalate, either solvent-free or its acetone complex (3·5 g.) in boiling petroleum (b. p. 100—120°; 600 c.c.) on cooling deposited needles, m. p. 183° (3·0 g.), $[\alpha]_D$ −107° (*c*, 1·990 in acetone; *l*, 1) (Found: equiv., by titration, 500. Calc. 498).

The Solvating Properties of the (+)- *and the* (−)-1 : 2 : 2 : 2-*Tetraphenylethyl Hydrogen Phthalate contrasted with the Non-solvation of the* (±)-*Isomeride.*—Equal weights (0·5 g.) of the (+)- and the (−)-hydrogen phthalate (each dissolved in 15 c.c. of acetone) were mixed; the solution slowly deposited large flat prisms of the (±)-isomeride, m. p. 219° alone and mixed with an authentic specimen (Found: equiv., 501. Calc., for solvent-free compound: equiv., 498). The isomeride was optically inactive.

Determinations of Molecular Weight.—A solution of (+)-1 : 2 : 2 : 2-tetraphenylethyl hydrogen phthalate (0·2318 g.) in nitrobenzene (24·0 g.) gave a depression of freezing point of 0·133°, whence M = 510. The corresponding (±)-compound (0·3495 g.) in nitrobenzene (23·8 g.) gave a depression of 0·170°, whence M = 610 (Calc. for $C_{34}H_{26}O_4$: M, 498).

Barium Salts of (−)- *and* (±)-1 : 2 : 2 : 2-*Tetraphenylethyl Hydrogen Phthalate.*—A solution of the (−)-hydrogen phthalate (0·5 g.) in warm acetone was neutralised with baryta: the crystals (0·5 g.) which slowly separated formed rosettes of fine needles, m. p. 213—216° (decomp.), from aqueous acetone. The corresponding (±)-isomeride also had m. p. 213—216°.

Each of these *salts*, when heated in a current of air as previously described, yielded acetone 2 : 4-dinitrophenylhydrazone, corresponding to 1·7 mol. of acetone [Found: M, by estimation of Ba (−)-isomeride, 1245; (±)-isomeride, 1235. $(C_{34}H_{25}O_4)_2Ba,2COMe_2$ requires M, 1247].

Thanks are expressed to Imperial Chemical Industries Limited and to the Central Research Funds Committee of the University of London for grants: also to Dr. A. I. Vogel of Woolwich Polytechnic for the provision of laboratory facilities.

Battersea Polytechnic, London, S.W.11.
Woolwich Polytechnic, London, S.E.18.

[*Received, November 24th*, 1953.]

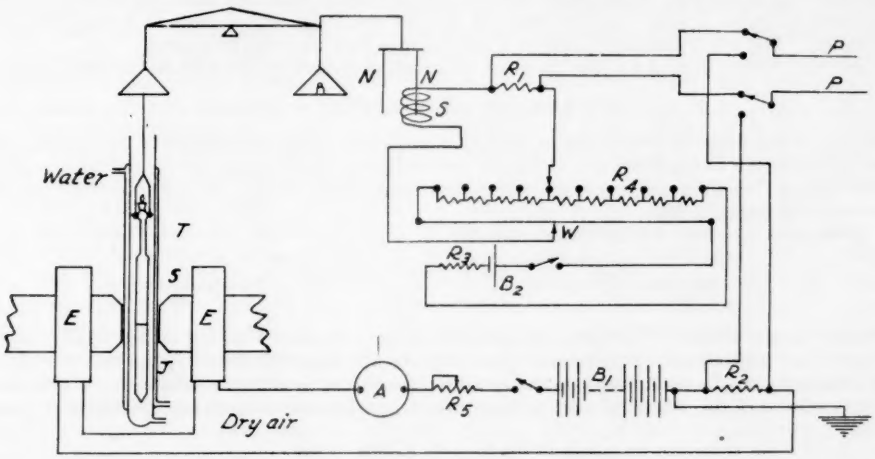
Magnetic Susceptibility as measured by Gouy's Method with the Specimen in a Fixed Position.

By O. M. Hilal and G. E. Fredericks.

[Reprint Order No. 4124.]

A refinement of Gouy's method of measuring magnetic susceptibilities is described, the position of the specimen in the magnetic field being fixed. The value for benzene was determined at 20°, water being the reference standard. The results indicate a reproducibility of better than 0·04% and the value for benzene was $10^6\chi^{20} = -0{\cdot}7012 \pm 0{\cdot}0002$.

While making measurements with a standard type of semimicro-balance and a moderately strong electromagnet (cf. *Proc. Phys. Soc.*, 1933, **45**, 425), it was observed that the use of the method of swings, for determining the fourth and later decimal places, was not entirely dependable when the interpole distance was made large enough to accommodate a double-walled jacket *J* (see Figure), controlling the temperature of the specimen, for, unless



a very large electromagnet is used, the bottom of the tube swings out of the region in which the field is uniform. It therefore appeared desirable, both for reproducibility and for flexibility of the apparatus, to use a true balance and hence a fixed specimen position. The physical dimensions of any tubes, jackets, or other parts placed between the poles would then not be so restricted.

Experimental

With the above object, an electro-dynamic balancing device was added, consisting of two ordinary sewing needles (*N*, *N*, see Figure), a small solenoid *S*, and a means of adjusting and measuring a current in the solenoid. The two needles were magnetized in opposite directions. They were then rigidly mounted in a vertical position on an arm of stiff wire which was attached to the bar carrying the automatic riders and which rested on the right-hand knife edge. The position of the needles is thus not affected by the position of the weights on the right-hand pan. The two needles are parallel, one lying along the axis of the solenoid and the other just outside it. As the two needles are magnetized in opposite directions, the forces exerted on them by a current in the solenoid are complementary, but, if they are magnetically exactly alike, the system as a whole will be insensitive to stray fields from outside the balance case. Best results were obtained with needles selected from the same package and checked for equal length (61 mm.) and equal diameter (1·17 mm.). With these, the effect of the stray field from the electromagnet, *E* mounted below the balance, was less than 0·03 mg. This was eliminated

completely by hanging a hook of fine steel wire, magnetized in the correct direction, on one of the pan supports. Its length was adjusted until there was no permanent deflection of the balance when the electromagnet was turned on.

The solenoid winding, 20 mm. long with an internal diameter of 13 mm., consists of 100 turns of 0·55-mm. D.S.C. copper wire. The current for the solenoid is provided by the battery B_2, and is controlled by the potential dividing action of the resistor R_3 and potentiometer $(R_4 + W)$, W being a slide wire. The solenoid is rigidly mounted, by means of a brass strap, on the inside of the balance case. Its vertical position is such that it exerts maximum force on the needles. With this arrangement, a current of 30 mA exerts a force of 10 mg. on the needles. This was selected as its maximum range so that it is used to indicate the third to the (estimated) sixth decimal place, the current being measured with a series resistance, R_1, and an accurate potentiometer connected at P,P. The same potentiometer, in combination with a shunt, R_2, is used to standardize the current through the electromagnet, supplied by the battery B_1 and controlled by the rheostat R_5 and ammeter A. For the indicated range, the force on the needles was found to be proportional to the solenoid current, to within the accuracy of measurements, which was better than 0·01 mg. The calibration was made with a set of certified standard weights.

A compensated Pyrex-glass specimen tube T was used to eliminate the temperature susceptibility coefficient of the glass and the air correction from the final calculations. The specimen chamber S was 1 cm. in diameter and 10 cm. long, with a neck of 2 mm. internal diameter. The lower chamber L had the same dimensions and was evacuated.

For a specimen in such a tube, the force, in dynes, produced by the field on the specimen is:

$$F = \tfrac{1}{2}A\kappa(H_1^2 - H_2^2) = 0{\cdot}981(f - f_1)$$

where A is the cross-sectional area of the specimen, κ its volume susceptibility, H_1 and H_2 are the field strength at the lower and the upper end of the specimen, respectively, f is the observed force (in mg.) on tube and specimen, and f_1 is a small force (in mg.) on the tube itself due to unavoidable imperfections.

From this equation, the mass susceptibility

$$10^6\chi = \frac{10^6\kappa V}{W} = \frac{2 \times 10^6 \times 0{\cdot}981 \times V}{A(H_1^2 - H_2^2)} \times \frac{f - f_1}{W} = \beta\frac{f - f_1}{W}$$

where W is the weight of the specimen filling the tube of volume V to the etched mark. Both β and f_1 are constants for a particular specimen tube and magnetic field; f_1 can be determined by measuring the forces (in mg.) on the specimen tube filled first with a substance (a) and then with a substance (b), where (a) and (b) have known but different volume susceptibilities. Then

$$f_1 = (\kappa_a f_b - \kappa_b f_a)/(\kappa_a - \kappa_b)$$

For the measurements recorded in this paper, water and air were selected for determinations of f_1, and water was used as a standard to evaluate β. The accepted values for these substances were used, *viz.*, $\kappa_{air} = 0{\cdot}029 \times 10^{-6}$, $\kappa_{water} = -0{\cdot}7187 \times 10^{-6}$, and $\chi_{water} = -0{\cdot}7200 \times 10^{-6}$, all at 20°. Three determinations of both the tube constant β and the mass susceptibility of benzene were made at 20° ± 0·02°. The benzene was purified by washing with concentrated sulphuric acid until colourless, then shaken with water. The product was dried ($CaCl_2$), shaken twice with mercury, twice recrystallised, and then dried and distilled over sodium. The results are listed in the following table:

	Tube constant, β	$-10^6\,\chi^{20}_{benzene}$
First filling	0·38263	0·7012
Second filling	0·38260	0·7014
Third filling	0·38266	0·7009
Mean value	0·38263	0·7012
,, deviation	±0·00003	±0·0002

French and Trew (*Trans. Faraday Soc.*, 1945, **41**, 437) found $-10^6\,\chi^{20}_{benzene} = 0{\cdot}7020 \pm 0{\cdot}0007$.

As the accuracy of the weights was ±0·01 mg., the above values are accurate to within 0·1%. The values indicate that the reproducibility of the apparatus is better than 0·04%.

FACULTY OF SCIENCE, ALEXANDRIA.

[*Received. February 25th*, 1953.]

The Crystal Structures of the Acid Salts of some Monobasic Acids. Part IV. Ammonium Hydrogen Disalicylate Hydrate.*

By T. C. Downie and J. C. Speakman.

[Reprint Order No. 4690.]

Acid salicylates of ammonium, potassium, and rubidium have been prepared, and studied by *X*-ray crystallographic methods. The compounds are isomorphous, and the structure of the ammonium salt has been fully investigated. This structure proves these salts to be monohydrates of the formula $MC_7H_5O_3,C_7H_6O_3,H_2O$ (M = NH_4, K, Rb), though the first two are probably identical with substances that had previously been described as anhydrous. The crystals are monoclinic, with four molecules of the above formula in a unit cell belonging to the space-group $P2_1/c$. The structural plan differs from that common to the acid salts described in the earlier papers of this series: the two salicylate residues are crystallographically distinct, and no apparently symmetrical hydrogen bonds are involved.

Acid salts of salicylic acid were first described by E. Hoffmann (*Arch. Pharm.*, 1878, **57**, 226; *Jahresber.*, 1878, 759), who prepared sodium, potassium, lithium, and ammonium compounds, gave the formula of the first as $NaC_7H_5O_3,C_7H_6O_3$, and implied that the formulæ of the others corresponded. Farmer (*J.*, 1903, **83**, 1444) also prepared the potassium salt and reported an analysis which supported the formula $KC_7H_5O_3,C_7H_6O_3$. Continuing our structural studies of acid salts (Part I, *J.*, 1949, 3357; Part II, *J.*, 1951, 185; Part III, *loc. cit.*), we have prepared potassium and ammonium hydrogen disalicylates which appear to be identical with the substances prepared by the earlier workers, and also a rubidium salt. These three compounds are isomorphous, and the crystal structure of the ammonium salt has been examined in detail. As with the acid salt described in Part II (*loc. cit.*), the structure shows that the compounds are in fact hydrated, *viz.*, (NH_4, K, Rb)$C_7H_5O_3,C_7H_6O_3,H_2O$. Because these acid salts crystallise incongruently from aqueous solutions containing a large excess of the neutral salt, it is difficult to purify them, so the results of analysis carried out in the usual way are not above suspicion. A detailed and exact study of the ternary phase diagram is therefore needed to establish their compositions by chemical means. Preliminary work on the system salicylic acid–potassium salicylate–water has been reported by N. Smith (Thesis, Sheffield, 1949), and further work is in progress. Hoitsema (*Z. physikal. Chem.*, 1898, **27**, 312) studied the ternary system involving sodium salicylate, and reported the " double salt " as $NaC_7H_5O_3,C_7H_6O_3$; but his work was not carried to the point when it could provide any definite evidence as to the hydration.

The acid salts studied in Parts I—III (*locc. cit.*) had structures based on a common plan. The structures of these acid salicylates prove to be quite different.

Experimental

Preparation of Materials.—Potassium hydrogen disalicylate is much more difficult to prepare than the other acid salts studied in this series. Attempts at preparation by the methods described by Hoffmann and Farmer were not successful: very often the crystals separating consisted of salicylic acid (which could easily be recognised by its oblique, 42°, extinction in polarised light), and under slightly different conditions a microcrystalline product of uncertain identity resulted. Suitable crystals of the acid salt (which shows straight extinction) were ultimately made by warming 1 g. of potassium carbonate and slightly over 2 g. of salicylic acid with about 8 c.c. of water or dilute aqueous alcohol. (These proportions correspond to a neutral salt, rather than to an acid one.) After the solution had cooled and been set aside, the free acid sometimes crystallised out first, but fine needles of the acid salt appeared later. The product had an equivalent that was a little high (320—340), but this was attributed to impurity due to the method of preparation. Purification by recrystallisation from alcohol was un-

* Part III, *J.*, 1954, 180.

trustworthy because of the likelihood of salicylic acid's separating out. However, single crystals of a size suitable for *X*-ray study could be obtained without great difficulty from the original preparation. In general, the material consisted of very fine needles, or bundles of needles, elongated in the direction of the *b*-axis. The only faces to be well developed were {001}, and there was ready cleavage parallel to (100). As the structure analysis proceeded, it became clear that the substance was potassium hydrogen disalicylate hydrate.

Ammonium hydrogen disalicylate hydrate was made in a similar way, concentrated ammonia solution being used instead of potassium carbonate. The substitution of rubidium carbonate led to rubidium hydrogen disalicylate hydrate, which was recognised to be such by its isomorphism with the other two. Several other crystalline substances, whose compositions were not investigated, were obtained with rubidium carbonate, and it appears that the system salicylic acid–rubidium salicylate–water may be fairly complex. It is just possible that the hydrated compound studied in this work may be a metastable phase.

Crystals of each of the three acid salts were examined by single-crystal rotation, oscillation and moving-film photographs, using Cu-$K\alpha$ radiation ($\lambda = 1{\cdot}54_2$ Å). Intensity data were obtained as described in Parts I—III, and similarly treated to give structure amplitudes.

Results.—Crystal data. The crystals belonged to the monoclinic prismatic class, and were closely isomorphous, with the following unit-cell dimensions:

	a, Å	*b*, Å	*c*, Å	β
$NH_4C_7H_5O_3,C_7H_6O_3,H_2O$	17·28 ± 0·05	3·89 ± 0·02	22·33 ± 0·05	98·8° ± 0·5°
$KC_7H_5O_3,C_7H_6O_3,H_2O$	16·90 ± 0·15	3·88 ± 0·05	22·40 ± 0·15	96·0° ± 1·0°
$RbC_7H_5O_3,C_7H_6O_3,H_2O$	17·13 ± 0·10	3·99 ± 0·02	22·74 ± 0·10	98·5° ± 0·5°

Further data for the ammonium compound were: $M = 311{\cdot}3$; vol. of unit cell = 1483 Å^3; *d* (found) 1·37, *d* (calc. by assuming four molecules of the above formula per unit cell) 1·39; F(000) = 656, absorption coefficient for Cu-$K\alpha$ *X*-rays = 10·97 cm.$^{-1}$.

Absent spectra for all three substances were: $h0l$ when l is odd; $0k0$ when k is odd. The space-group is thereby uniquely indicated to be $P2_1/c$ (C_{2h}^5). No molecular symmetry is required, and all atoms are in general positions. Centrosymmetry of the structure as a whole was confirmed by the Wilson (*Acta Cryst.*, 1949, **2**, 318) and the Rogers (*ibid.*, 1950, **3**, 210) test.

Structure amplitudes for the three principal zones of the ammonium compound are given in Tables 2 and 3.

Structure analysis. The very short *b*-axis suggested that the structure analysis could best be approached by way of the ($h0l$) projection. The potassium salt was first available, and a Patterson projection was calculated. The result was disappointing, as it did not even indicate the position of the "heavy" atom. A corresponding projection was then made for the rubidium salt; the highest peak, apart from that at the origin, did, in fact, signify the Rb–Rb vector, but, since this peak was only a little higher than some others, the result was felt to be uncertain until confirmed by carrying out a third projection with only the higher-order terms.

The *x*- and *z*-co-ordinates of the rubidium atoms now being known, it became possible to calculate their contributions to the structure factors, and hence to assess the possible signs of 223 terms. These were used to calculate an electron-density projection. Despite some blemishes, this projection could have led to the correct structure. It did not, in fact, do so because of the presence of a large peak, due to the water molecule, which could not be interpreted at the time.

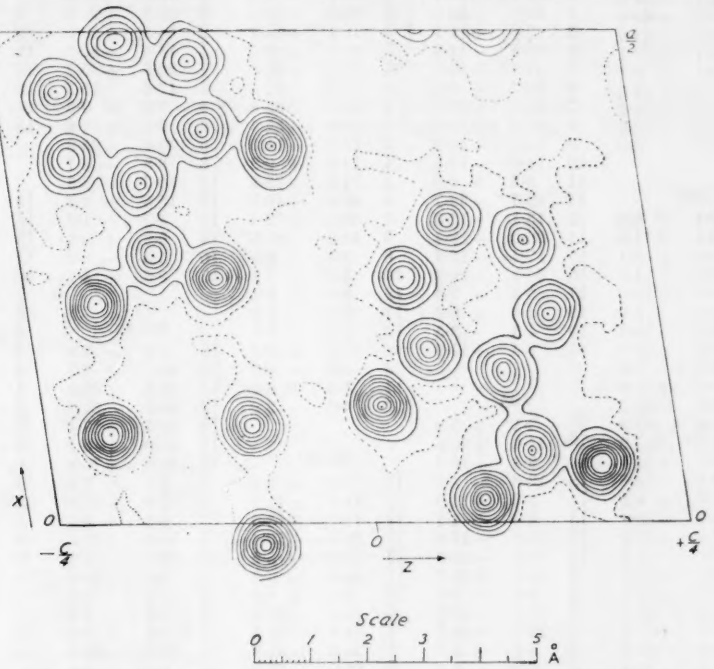
Another approach was more successful. Experience with similar compounds had suggested a *ratio* of about 1·8 between the average structure amplitudes for rubidium and potassium isomorphs; and knowing the position of the cation and assuming it to be exactly the same in both cells, the *difference*, on an absolute scale, between individual pairs of structure factors could be calculated. Hence, by considering statistically a large number of terms for which this difference was significant, it was possible to place both sets of data on an approximately absolute scale. The scheme could then be extended to the ammonium salt, so as to put its structure factors on to the same scale and to decide the signs of 75 of them. A Fourier synthesis was made, and the resulting map could be interpreted without difficulty; the indication of the presence of an unexpected water molecule was now unmistakable. This view of the structure was refined by repeated syntheses until the final electron-density map, shown in Fig. 1, was achieved. The interpretation of this map and the numbering of the atoms are indicated in Fig. 2(*a*).

The peak attributed to the ammonium ion is only a little lower than that attributed to the

water molecule, and the assignment might well have been in doubt. However, a similar electron-density projection was made for the potassium compound, and it was unequivocal in placing the potassium ion in a position equivalent to that of the ammonium in Fig. 2(*a*).

All the atoms (apart from hydrogen) are well resolved in Fig. 1, and the co-ordinates derived

FIG. 1. *Ammonium hydrogen disalicylate hydrate: electron-density projected along* b-*axis.*



(Contour-line scale: 1 electron per sq. Å; line of unit electron-density broken.)

TABLE 1. *Atomic co-ordinates.* [See Fig. 2(*a*) for numbering of atoms. Origin at a centre of symmetry; *x*, *y*, and *z* as fractions of the cell-edges; *X'*, *Y*, and *Z'* in Å, and referred to orthogonal axes, with *X'* parallel to *x*.]

	x	*y*	*z*	*X'*	*Y*	*Z'*
NH_4^+	0·0992	0·000	−0·0863	2·02	0·00	−1·91
H_2O	0·0906	−0·380	−0·1994	2·25	−1·48	−4·41
O(1)	0·2237	0·243	−0·1949	4·54	0·95	−4·31
O(2)	0·2491	0·2925	−0·0951	4·64	1·14	−2·10
O(3)	0·3834	0·069	−0·0366	6·76	0·27	−0·81
O(4)	0·0587	0·650	0·1878	0·37	2·53	4·14
O(5)	0·0208	0·500	0·0892	0·06	1·95	1·97
O(6)	0·1163	0·530	0·0187	1·95	2·06	0·41
C(1)	0·2740	0·189	−0·1439	5·23	0·74	−3·18
C(2)	0·3475	0·033	−0·1445	6·51	0·13	−3·19
C(3)	0·3678	−0·067	−0·2007	7·05	−0·27	−4·43
C(4)	0·4398	−0·222	−0·2023	8·29	−0·87	−4·47
C(5)	0·4893	−0·272	−0·1490	8·97	−1·06	−3·29
C(6)	0·4702	−0·174	−0·0937	8·45	−0·68	−2·08
C(7)	0·3976	−0·018	−0·0915	7·18	−0·08	−2·03
C(8)	0·0718	0·604	0·1327	0·79	2·35	2·93
C(9)	0·1505	0·676	0·1177	2·20	2·63	2·60
C(10)	0·1753	0·643	0·0621	2·82	2·50	1·37
C(11)	0·2497	0·716	0·0505	4·14	2·79	1·12
C(12)	0·3073	0·825	0·0939	4·99	3·21	2·07
C(13)	0·2862	0·865	0·1513	4·43	3·37	3·34
C(14)	0·2115	0·794	0·1624	3·10	3·09	3·58

TABLE 2. *Observed structure amplitudes and calculated structure factors for h0l.* (In each set of three columns, the first lists values of h, the second $|F_O|$, and the third F_C.)

	*h*00		$\bar{4}$	65·1	−74·5	$\bar{11}$	10·2	−10·1	$\bar{8}$	16·0	+14·7
1	(?)	+35·7	$\bar{3}$	36·3	−45·5	$\bar{9}$	20·3	−22·5	$\bar{7}$	42·9	+40·7
2	26·0	−26·4	$\bar{2}$	29·8	+27·4	$\bar{8}$	24·8	−31·8	$\bar{6}$	4·3	− 1·6
4	5·9	+ 1·9	$\bar{1}$	33·2	+47·8	$\bar{7}$	12·9	−19·4	$\bar{5}$	29·6	−31·6
5	34·7	−34·0	0	101·1	−136·1	$\bar{5}$	11·4	+ 6·6	$\bar{4}$	71·6	+69·6
6	59·1	−65·6	1	34·9	−38·8	$\bar{4}$	33·9	−39·6	$\bar{3}$	26·4	+21·8
7	46·8	−43·6	3	7·9	+11·1	$\bar{3}$	10·1	+14·1	$\bar{2}$	14·5	+10·2
8	34·1	+37·1	4	48·4	−44·2	$\bar{2}$	51·8	+49·5	$\bar{1}$	13·4	−16·1
9	8·3	− 9·7	5	37·2	+49·1	$\bar{1}$	37·9	+39·3	1	30·5	+30·2
11	13·5	+16·5	6	10·2	− 4·2	0	57·1	−57·5	3	12·6	−15·2
13	14·4	+13·2	7	22·2	−21·3	1	65·0	−62·8	4	7·9	− 0·6
15	15·0	−10·4	8	17·4	+16·9	2	56·0	−42·4	5	9·5	+11·4
21	7·0	− 3·0	9	14·1	+10·2	3	13·4	−11·9	6	27·4	+25·8
			10	14·6	−18·5	4	11·2	+ 9·8	8	9·8	− 8·7
	*h*02		11	9·3	+ 5·0	5	74·0	−73·8	11	10·7	− 8·6
			12	42·7	−39·7	6	46·8	+46·3	12	15·5	− 4·2
$\bar{33}$	6·4	− 6·0	13	15·1	−12·3	7	68·5	+72·3	13	5·2	− 1·3
$\bar{20}$	8·4	+11·6	14	29·3	−28·4	8	44·8	+47·3	14	6·2	+ 5·4
$\bar{18}$	5·5	+ 6·1	15	17·4	−17·4	9	5·5	+ 4·5	16	5·5	− 5·4
$\bar{17}$	16·0	+14·5	16	20·1	+20·2	10	4·3	− 1·1	17	5·5	+ 4·7
$\bar{16}$	9·8	+15·0	17	9·3	− 7·6	12	8·3	− 3·1			
$\bar{15}$	3·3	+ 4·0	18	4·8	+ 6·6	13	8·8	− 9·3			
$\bar{14}$	26·9	−33·8	20	4·3	− 3·5	14	9·5	+ 7·7		*h*0,14	
$\bar{13}$	27·4	−23·2	21	8·4	+11·9	15	16·7	+18·0	$\bar{16}$	5·5	− 7·8
$\bar{12}$	6·2	− 7·4				16	3·8	− 0·9	$\bar{15}$	10·2	+ 6·7
$\bar{10}$	23·1	+31·3				17	5·2	+ 6·9	$\bar{14}$	26·8	+30·5
9	35·1	−33·2		*h*06		18	4·0	− 2·9	$\bar{13}$	35·1	−37·8
8	92·4	+107·9	$\bar{21}$	3·1	+ 4·8				$\bar{12}$	25·5	+27·1
7	96·0	+115·9	$\bar{18}$	44·6	+30·6		*h*0,10		$\bar{11}$	47·0	+48·1
6	25·1	+22·5	$\bar{16}$	9·8	−12·3				$\bar{10}$	30·6	+36·3
5	9·1	− 5·6	$\bar{15}$	10·0	− 9·7	$\bar{18}$	7·4	− 8·7	9	7·4	− 7·3
4	7·6	+ 8·9	$\bar{14}$	3·3	− 2·9	$\bar{15}$	11·2	−11·1	8	17·9	−17·5
3	29·8	−44·1	$\bar{13}$	6·0	+ 4·1	$\bar{14}$	11·2	−14·6	7	8·8	+ 4·4
2	52·6	+93·0	$\bar{12}$	15·8	−15·9	$\bar{13}$	22·9	+27·4	6	14·8	+11·1
$\bar{1}$	(?)	−14·7	$\bar{11}$	19·3	−18·7	$\bar{12}$	15·0	− 5·2	5	26·7	−28·1
0	(?)	−13·0	9	23·8	+21·6	$\bar{11}$	11·6	− 9·9	4	9·3	+10·6
1	27·2	+25·1	8	3·4	− 3·8	$\bar{10}$	8·3	+ 8·0	3	7·4	− 4·9
2	66·8	−115·5	7	32·0	−30·9	9	26·5	+36·3	2	4·3	− 3·0
3	22·4	+27·1	6	37·7	−33·9	8	18·6	−23·5	$\bar{1}$	5·0	+ 2·3
4	60·0	−62·5	5	5·5	− 9·6	7	34·6	−34·8	1	12·0	−10·6
5	8·1	+20·4	4	6·2	− 0·4	6	65·0	−70·9	4	9·8	− 0·2
7	30·0	−27·6	3	56·7	−55·6	4	19·8	−16·6	5	17·0	− 9·2
8	7·2	−13·9	2	1·7	− 1·4	3	18·4	+20·2	6	5·0	+ 4·8
9	12·6	+17·4	$\bar{1}$	21·0	−24·8	2	67·3	+76·3	7	6·0	− 1·0
10	3·3	− 4·3	0	6·7	− 3·3	$\bar{1}$	40·6	+35·8	8	4·8	+ 1·7
12	12·4	+11·8	1	20·0	+15·5	0	55·0	+54·1	9	10·0	+10·4
13	17·9	+16·5	2	32·9	−28·2	1	39·2	+29·5	10	18·4	−19·6
14	45·7	−40·4	3	46·3	+37·4	2	11·7	+ 3·1	11	11·4	− 8·4
16	8·6	+ 5·0	4	17·2	−17·6	3	19·3	−18·5	12	6·4	− 7·4
18	14·8	−13·0	5	29·1	−29·7	5	12·2	+ 5·6	13	4·8	+ 3·0
19	5·5	− 6·4	6	10·0	+12·6	6	9·8	+ 5·2	15	8·8	−11·7
20	8·4	−11·4	7	35·4	−35·8	7	23·8	+22·1	16	6·0	− 5·4
21	2·6	− 5·4	8	16·2	−16·1	8	15·5	+10·7			
			9	27·1	−21·0	9	31·4	+28·7			
	*h*04		10	6·4	+ 1·1	13	7·9	+10·4		*h*0,16	
			11	4·8	+ 6·2	14	9·3	− 8·9	$\bar{19}$	8·8	+ 7·5
$\bar{33}$	4·3	− 6·6	12	28·1	−27·7	15	10·0	−11·1	$\bar{18}$	18·6	+16·6
$\bar{20}$	7·6	− 7·4	13	30·6	−29·8	18	8·8	− 7·1	$\bar{17}$	9·3	+10·6
$\bar{18}$	4·5	+ 7·9	14	71·0	+66·6				$\bar{15}$	9·3	−11·4
$\bar{17}$	11·9	+11·0	15	24·6	+18·3				$\bar{14}$	7·4	+ 6·6
$\bar{16}$	12·4	+ 7·7	16	10·1	+11·2		*h*0,12		$\bar{11}$	13·6	+ 8·7
$\bar{15}$	10·0	+ 4·4	18	7·2	+ 7·5	$\bar{20}$	9·1	+12·0	$\bar{10}$	15·8	−16·1
$\bar{14}$	16·2	+11·6	20	6·9	− 9·3	$\bar{19}$	5·2	+ 7·8	9	7·9	− 5·4
$\bar{13}$	5·7	+ 5·0				$\bar{18}$	3·6	− 4·7	8	13·8	− 6·4
$\bar{12}$	10·0	+11·8				$\bar{17}$	8·8	+ 9·8	7	7·2	− 7·8
$\bar{11}$	9·1	− 6·2		*h*08		$\bar{16}$	9·1	−11·8	6	7·4	− 4·9
$\bar{10}$	22·9	+28·2	$\bar{19}$	10·0	−11·3	$\bar{15}$	5·3	+ 6·2	5	9·8	− 2·5
9	35·7	+41·6	$\bar{17}$	5·2	− 7·5	$\bar{14}$	34·9	−35·1	4	4·8	− 3·3
8	7·4	− 4·9	$\bar{16}$	10·0	−11·6	$\bar{13}$	21·2	−22·9	3	15·8	−11·8
7	15·3	+18·3	$\bar{15}$	7·2	+ 7·6	$\bar{11}$	8·1	− 5·2	2	5·7	+ 3·0
6	29·1	−33·6	$\bar{14}$	6·7	+ 6·9	$\bar{10}$	31·0	+32·9	0	21·3	−26·3
5	15·1	+16·3	$\bar{13}$	9·5	−11·9	9	21·0	+19·4	1	45·4	+47·8
									3	27·7	−17·0
									4	15·8	−14·5
									5	11·2	+ 9·8
									6	8·6	− 0·6
									7	16·0	−13·3
									8	32·0	−33·8
									10	22·2	−20·3
									11	8·6	−10·1
									12	11·7	+11·3
									13	3·3	+ 2·9
									14	10·0	+11·8
									15	5·3	+ 6·4
										*h*0,18	
									$\bar{15}$	4·5	− 2·9
									$\bar{14}$	9·8	− 7·1
									$\bar{13}$	3·2	+ 4·6
									$\bar{11}$	17·9	−14·6
									$\bar{10}$	19·8	−27·5
									9	8·3	+ 5·8
									8	14·4	−17·5
									6	23·4	+20·4
									5	11·2	+15·0
									4	4·5	+ 1·4
									3	11·4	+13·6
									2	8·8	−12·6
									$\bar{1}$	19·6	+17·8
									0	46·5	−46·0
									1	28·8	−28·1
									2	23·1	−19·7
									3	42·5	−41·7
									4	16·0	+12·7
									5	16·5	+ 7·7
									6	12·4	+13·6
									7	22·7	+24·8
									9	12·4	−12·4
									12	5·5	+ 4·3
									13	4·5	− 5·2
									14	2·9	+ 1·4
										*h*0,20	
									$\bar{17}$	10·4	−14·4
									$\bar{15}$	7·6	− 8·0
									$\bar{13}$	6·7	+ 9·3
									$\bar{12}$	9·3	+ 5·4
									$\bar{11}$	16·2	+15·3
									$\bar{10}$	7·2	− 6·9
									9	6·2	+ 5·6
									7	25·8	−29·3
									6	16·0	−15·2
									5	15·5	−14·9
									3	5·7	+ 1·3
									2	11·0	− 9·8
									$\bar{1}$	13·1	+10·6
									0	29·6	+34·6
									1	35·8	−39·5
									2	13·1	− 9·2
									3	10·0	+ 9·0
									4	42·2	+32·2
									5	9·1	+ 5·3
									6	5·5	− 3·6
									7	9·8	+12·9
									8	9·8	+12·0
									10	4·1	+ 2·6
										*h*0,22	
									$\bar{15}$	5·5	− 6·3
									$\bar{14}$	10·8	−10·9
									$\bar{12}$	7·6	+ 6·7

TABLE 2. (*Continued.*)

	*h*0,22		$\bar{1}$	3·4	− 2·2	$\bar{1}\bar{3}$	6·0	+ 8·6	3	9·5	− 4·2	0	2·6	− 1·9
$\bar{1}\bar{1}$	3·6	+ 2·0	0	11·2	+ 8·4	$\bar{1}\bar{0}$	7·9	+ 7·7	4	10·8	−11·8	1	5·7	− 0·5
$\bar{1}\bar{0}$	5·2	− 5·6	1	6·7	+ 3·3	$\bar{8}$	4·1	− 5·6	5	4·3	+ 6·0	3	11·0	+10·8
$\bar{9}$	13·1	−14·3	2	6·0	+ 3·8	$\bar{6}$	5·0	+ 3·0	6	9·8	− 9·9	5	3·1	+ 2·8
$\bar{8}$	16·7	+14·4	3	8·8	+ 9·6	$\bar{5}$	12·2	+11·5	8	6·4	+ 5·1			
$\bar{6}$	16·0	−10·2	4	7·9	+ 5·3	$\bar{4}$	3·1	− 0·1					*h*0,28	
$\bar{5}$	10·5	− 7·6	8	6·4	− 6·7	$\bar{3}$	11·4	+ 9·2		*h*0,26		$\bar{3}$	5·7	+ 6·8
$\bar{4}$	15·6	+16·3				$\bar{2}$	8·4	+ 6·9	$\bar{1}\bar{0}$	6·0	+ 5·7	$\bar{1}$	5·0	− 4·7
$\bar{3}$	25·5	+22·5		*h*0,24		$\bar{1}$	3·8	+ 3·8	$\bar{9}$	6·4	+ 3·7	0	15·3	−16·9
$\bar{2}$	4·1	+ 7·0	$\bar{1}\bar{4}$	8·3	+ 9·1	1	7·2	− 4·2	$\bar{3}$	9·8	−11·0			

from it were corrected for termination-of-series errors by Booth's method ("Fourier Technique in X-Ray Organic Structure Analysis," Univ. Press, Cambridge, 1948, p. 100) to yield the x and z-co-ordinates listed in Table 1.

FIG. 2(*a*).

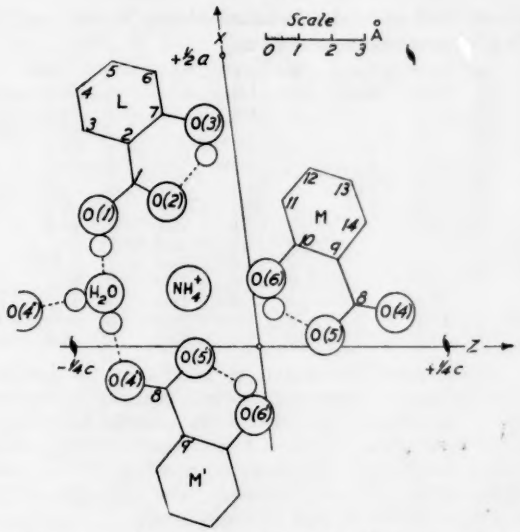


FIG. 2(*b*).

FIG. 2(*a*). *Ammonium hydrogen disalicylate hydrate: numbering of atoms and interpretation of Fig.* 1 (The centres of symmetry shown are at $y = 0$ and $\frac{1}{2}b$.)

FIG. 2(*b*). *Sketch of the immediate environment of the ammonium ion.*

In the earlier stages of the analysis, the atomic scattering factors used were those given in Part I, the factor for nitrogen being taken to be the same as that for oxygen. As the refinement proceeded, these factors were modified by a method essentially the same as that described by Luzzati (*Acta Cryst.*, 1953, **6**, 158), and the scattering functions which best fitted the data were as follows:

$2 \sin \theta$	0·00	0·25	0·50	0·75	1·00	1·25	1·50	1·75
f_C	(6·00)	5·02	3·63	2·37	1·54	1·04	0·76	0·57
f_N	(7·00)	6·53	4·94	3·14	1·89	1·44	1·09	0·79
f_O	(8·50)	6·61	4·99	3·55	2·40	1·64	1·14	0·79

By using these factors and the co-ordinates listed in Table 1, values of F($h0l$) were calculated, and they are compared with the observed amplitudes in Table 2. To economise space, unobserved reflexions are omitted; the calculated values for these were almost always insignificant. (The only noteworthy exceptions were 204, 10,0,10, and $\bar{5}$,0,10, for each of which $|F_o|$ was $<3·5$, and for which F_c was respectively $+8·8$, $-7·3$, and $-7·6$.) The 366 observed terms represent 71% of those accessible. If 004, 202, and $20\bar{2}$, which are apparently affected by extinction errors, are omitted, the discrepancy, R, is 16·9%.

The determination of the y-co-ordinates from F($0kl$) and F($hk0$) data had to be made by

trial-and-error methods, since the atoms would be insufficiently resolved in the *a*- and *c*-axis projections to permit of a useful application of the Fourier series method. Some guidance as to the position of the ammonium ion was, however, obtained from a "difference Patterson" synthesis, the terms for which were the absolute-scale values of $(F^2_{Rb} - F^2_{NH_4})$ for the 0*kl*-zone. This synthesis indicated that the cations were not far from the positions, $y = 0$ and $\frac{1}{2}b$. The unit cell contains centres of symmetry and 2_1-axes, which cannot be distinguished in a *b*-axis projection. Packing considerations led to the conclusion that a centre must lie between 0(5) and 0(5′), and this point was taken for origin as implied in Fig. 2(*a*). The details of the structure in the *y*-dimension were elucidated by empirical methods, the salicylate residues being assumed planar and the distances between the ammonium ion and the surrounding oxygen atoms not less than 2·8 Å. The *y*-co-ordinates finally adopted are included in Table 1. Observed structure amplitudes for (0*kl*) and (*hk*0) are compared in Table 3 with structure factors calculated with the atom-scattering functions already given. Reflexions not observed are again omitted. In nearly all such cases F_C was very small, the principal exceptions being 028, 0,2,13, and 820. The values of *R* for these zones are respectively 22·9% and 21·0%.

TABLE 3. *Observed structure amplitudes and calculated structure factors for* 0kl *and* hk0. (See Table 2 for arrangement of data.)

	01*l*		20	10·4	− 3·3	10	16·4	+ 3·1	8	12·4	+22·1		*h*20	
1	12·4	+10·9	21	5·2	+ 9·2	11	10·4	−12·2	12	11·9	−10·4	1	22·4	+23·6
2	94·2	+99·7	24	5·2	+ 5·4	12	13·4	+ 9·0	14	11·8	+ 5·8	2	29·9	+48·7
3	30·3	−19·8	25	7·3	+ 6·7	14	4·2	+ 2·1				3	40·7	+45·0
4	15·2	+27·1	27	6·7	+ 5·0	15	8·5	+15·2				4	68·1	−76·1
5	23·1	+24·1				16	15·0	−12·1		*h*10		9	15·4	+ 3·4
8	21·3	+26·3		02*l*		17	10·0	−11·3	1	39·4	+50·2	10	17·3	+22·8
9	19·2	−14·5	0	6·4	− 7·7	18	11·0	−12·1	2	45·4	+36·9	11	26·7	+15·5
10	8·3	− 8·4	2	25·6	+37·2	19	6·0	− 9·4	3	67·1	+75·4	12	19·6	− 7·1
11	8·3	− 8·0	3	22·5	−15·2				4	13·1	+ 5·2			
12	8·3	+ 2·5	4	15·6	+17·5				5	19·6	+ 9·9		*h*30	
13	15·0	+13·6	5	16·4	−14·1		03*l*		6	29·8	−31·8	1	13·1	+16·4
14	5·8	− 2·3	6	14·3	−14·3	4	8·5	+ 9·8	7	48·6	+48·3	2	11·2	+21·4
15	17·8	−16·3	7	19·2	+13·8	5	13·4	− 2·1	9	19·6	−20·4	4	9·8	+14·3
17	21·6	−17·0	9	22·5	+21·4	6	9·8	+ 8·3	10	21·0	−18·5	5	7·9	+11·7

It is considered that the *x*- and *z*-co-ordinates are unlikely to be in error by more than 0·02 Å. The *y*-co-ordinates are less certain, but—in an asymmetric unit containing 22 atoms—the above measure of agreement seems to be adequate evidence of the essential correctness of the structure found. Bond-lengths, which are given in Table 4, are relatively little affected by small errors in the *y*-co-ordinates; they should generally be correct to within 0·05 Å. Intermolecular distances between non-bonded atoms are not abnormal. The salicylate residues, *L* and *M*, of Fig. 2(*a*), are inclined to (010) at about 25° and 11° respectively.

TABLE 4. *Principal interatomic distances* (Å) *and certain bond-angles.*

C(1)–C(2)	1·42	C (8)–C(9)	1·48	O(1) . . . O(2)	2·22	O(4) . . . O(5)	2·27
C(2)–C(3)	1·40	C (9)–C(10)	1·38	O(2) . . . O(3)	2·63	O(5) . . . O(6)	2·45
C(3)–C(4)	1·39	C(10)–C(11)	1·38				
C(4)–C(5)	1·37	C(11)–C(12)	1·35	O(1) . . . H_2O	2·76 (3·34)	NH_4^+ . . . O(2)	2·87 (3·81)
C(5)–C(6)	1·38	C(12)–C(13)	1·39	NH_4^+ . . . H_2O	2·91 (3·48)	NH_4^+ . . . O(6)	2·95 (3·10)
C(6)–C(7)	1·40	C(13)–C(14)	1·38	H_2O . . . O(4′)	2·65 (3·87)	NH_4^+ . . . O(5′)	2·84 (2·84)
C(7)–C(2)	1·37	C(14)–C(9)	1·41	H_2O . . . O(4″)	2·65 (3·90)		
C(1)–O(1)	1·34	C (8)–O(4)	1·29				
C(1)–O(2)	1·29	C (8)–O(5)	1·27				
C(7)–O(3)	1·33	C(10)–O(6)	1·37				

<O(1)–C(1)–O(2)	115°	<O (4)–C (8)–O (5)	124°	<O(4′) . . . H_2O . . . O(4″)	99°
O(1)–C(1)–C(2)	122	O (4)–C (8)–C (9)	120	O(1) . . . H_2O . . . O(4″)	105
C(2)–C(1)–O(2)	124	C (9)–C (8)–O (5)	116	O(1) . . . H_2O . . . NH_4^+	108
C(1)–C(2)–C(7)	120	C (8)–C (9)–C(10)	127	O(4′) . . . H_2O . . . NH_4^+	92
C(2)–C(7)–O(3)	125	C (9)–C(10)–O (6)	112		
C(6)–C(7)–O(3)	116	C(11)–C(10)–O (6)	123		

DISCUSSION

In the structures of the acid salts described in Parts I—III (*locc. cit.*), the metallic cations and acidic hydrogen atoms are in special positions. The hydrogen bond is effectively symmetrical, and the two acid residues are crystallographically equivalent, so that free acid, HA, and anion, A^-, cannot be distinguished by *X*-ray methods. The

salicylate structure, on the other hand, has all atoms in general positions, and the acid residues are crystallographically distinct. Indeed, there appear to be reasons for regarding residue *L* as corresponding to HA, and *M* to A^-. The difference between the bond lengths C(1)–C(2) and C(8)–C(9) is almost certainly real, and it is in the sense required by the distinction; and in so far as they are collectively significant, the same applies to the C–O lengths, to the valency-angles round C(1) and C(8), and to the distances O(2) . . . O(3) and O(5) . . . O(6). (It is presumed that there will be considerable co-ordination between the C=O bond and the benzene ring in HA, but that this co-ordination will be diminished in A^- on account of the cross-co-ordination between the carboxylic oxygen atoms.)

In a few ammonium compounds (*e.g.*, the fluoride) the ammonium ion has a tetrahedral environment of electronegative atoms, and its four hydrogens will certainly be engaged in forming hydrogen bonds with its four neighbours. Far oftener there are more than four nearest neighbours co-ordinated round the ammonium ion (*e.g.*, in the sulphate), and this will be the situation when there is strict isomorphism with a potassium compound (*e.g.*, potassium sulphate). This point has been discussed by Wells (" Structural Inorganic Chemistry," Univ. Press, Oxford, 1950, pp. 245, 246; see also van Niekerk and Schoening, *Acta Cryst.*, **1952**, **5**, 475). In the acid salicylates, each cation is surrounded by six approximately equidistant (see Table 4) oxygen atoms, whose situations at the corners of a somewhat irregular trigonal prism are suggested in Fig. 2(*b*). The N . . . O distances are consistent with the ionic radius, 1·48 Å, for ammonium suggested by Pauling (" Nature of the Chemical Bond," Univ. Press, Cornell, 1940, p. 350). The four nearest neighbours of each water molecule are in a tetrahedral arrangement, and the angles at H_2O quoted in Table 4 refer to this environment.

Since the ammonium and potassium (or rubidium) salts are so closely isomorphous, it seems that only such hydrogen bonds should be postulated in the ammonium compound as could also occur in the potassium compound. It is, therefore, inferred that the acidic hydrogen atom from one of the salicylate residues has been taken over by the ammonium ion, and that no significant hydrogen-bonding can exist between that ion and its surroundings. The structure would then involve five hydrogen bonds per stoicheiometric molecule, NH_4A,HA,H_2O. This is equal to the number of protons available, *viz.*, one from the remaining acid hydrogen atom, two from the phenolic groups, and two from the water molecule. Although hydrogen atoms were not detected in this work, it seems reasonable to suggest (cf. Donohue, *J. Phys. Chem.*, 1952, **56**, 502) that they may be disposed as indicated in Fig. 2(*a*), with residue *L* in the rôle of neutral acid, HA, and *M* in that of anion, A^-. The chief difference in unit-cell dimensions in going from the ammonium to the potassium salt lies in the *a*-parameter. The radius of K^+ being less than that of NH_4^+, the reduction observed is to be expected, since the shortest contact, that between cation and O(5), would be most affected, and this lies nearly in the direction of the *a*-axis.

Cochran (*Acta Cryst.*, **1953**, **6**, 260) has recently published an account of a very precise determination of the structure of salicylic acid. The present work is necessarily much less exact; but the bond-lengths shown in Table 4 are not inconsistent with Cochran's values.

We are glad to express our thanks to Professor J. M. Robertson, F.R.S., in whose laboratories this work was carried out, for his interest and encouragement. We are indebted to the Department of Scientific and Industrial Research for a maintenance grant (to T. C. D.), and to Imperial Chemical Industries Limited for lending some of the apparatus used.

THE UNIVERSITY, GLASGOW, W.2. [*Received, October 2nd,* 1953.]

Homolytic Aromatic Substitution. Part V. Partial Rate Factors for the Phenylation of Diphenyl.*

By J. I. G. Cadogan, D. H. Hey, and Gareth H. Williams.

[Reprint Order No. 4741.]

The rate of phenylation of diphenyl relative to that of nitrobenzene by phenyl radicals (generated from benzoyl peroxide) has been measured, and the rate of attack relative to benzene calculated. The percentages of the 2-, 3-, and 4-isomerides formed in the phenylation of diphenyl have been measured by ultra-violet spectrophotometry, thus enabling the calculation of partial rate factors to be made. The values obtained are discussed with reference to the predictions of molecular orbital theory.

The determination of partial rate factors for the homolytic phenylation of nitrobenzene and the four halogenobenzenes was reported in Parts I—IV (I, Hey, Nechvatal, and Robinson, *J.*, 1951, 2892; II, Augood, Hey, and Williams, *J.*, 1952, 2094; III, *J.*, 1953, 44; Part IV *). In a discussion of these and other results by Hey and Williams (*Discuss. Faraday Soc.*, 1953, **14**, 216) it was pointed out that the theoretical prediction of partial rate factors for homolytic substitution in benzene derivatives containing a hetero-substituent is dependent upon the somewhat arbitrary choice of values for the parameters α_X and β_{O-X} for the hetero-atom X and the C–X bond. These difficulties, however, do not occur in hydrocarbons, in which cases more reliable predictions should be possible. The phenylation of the alkylbenzenes is complicated by the possibility of attack in the side-chain (Augood, Hey, Nechvatal, Robinson, and Williams, *Research*, 1951, **4**, 386), which renders these compounds unsuitable for an investigation of this type, since an estimate of the extent of side-chain attack must first be made. The phenylation of a series of alkylbenzenes will be the subject of later papers in this series. Polynuclear hydrocarbons, on the other hand, present practical difficulties on account of their low volatility, which renders impossible in most cases the separation of the various fractions of the mixture produced. In diphenyl, however, such a separation has been found to be possible.

The arylation of diphenyl by means of the Gomberg reaction has been studied qualitatively by Grieve and Hey (*J.*, 1938, 108), who allowed diphenyl in chloroform solution to react with diazotised aniline and *p*-nitroaniline, and in both cases isolated the 4-substituted isomeride from the product mixture. Once again (cf. Parts II and III, *locc. cit.*) the proportions of isomerides found in the present investigation do not bear out the results of the previous preparative experiments, owing to the fact that the very much lower solubility of the 4-isomeride had rendered extremely difficult the isolation of the 2- and 3-isomerides in Grieve and Hey's work.

Experimental Methods and Results

Determination of $\frac{Ph\cdot NO_2}{PhPh}K$.—Benzoyl peroxide (6 g.) was allowed to decompose in an equimolar mixture of nitrobenzene and diphenyl (200 g.) in a thermostat at 80° for 72 hr. The mixed product was isolated and the nitro-compound was determined therein by titration with titanous chloride. The standard procedure described in Part II (*loc. cit.*) was employed, except that in the chromatography step the column was eluted with a larger predetermined amount of benzene (300 ml.) in order to ensure the complete removal of the rather insoluble diphenylbenzenes. In the final distillation, fore-runs, *i.e.*, mixed fractions containing the last traces of diphenyl and the first traces of nitrodiphenyls, were collected separately from the nitrodiphenyl–diphenylbenzene product fractions, so that the latter should not be contaminated with the last traces of diphenyl. The fore-runs were analysed for nitrodiphenyls by titanous chloride titration, and a correction in terms of nitrodiphenyls applied to the composition of the nitrodiphenyl–diphenylbenzene fraction. A fraction taken immediately before the fore-run proved to consist entirely of diphenyl, showing that neither the fore-run nor the product fraction was contaminated with residual nitrobenzene. It may safely be assumed that the fore-runs contained no diphenylbenzenes, since these were found not to be distilled until a temperature 60° above that at which

* Part IV, *J.*, 1953, 3412.

the fore-runs were collected had been reached. The high-boiling residue left after completion of the distillation was of negligible weight. The results of these experiments (1—4) are given in Table 1. The proportion of benzoyl peroxide accounted for is lower than in previous cases (Parts II, III, IV) because of loss of benzoic acid which is distilled on removal of the unchanged diphenyl in the first stage of the working-up procedure.

TABLE 1.

Expt. No.:	1	2	3	4
Diphenylbenzene–nitrodiphenyl fraction (g.)	3·549	3·789	3·238	3·299
Nitrodiphenyl (%)	47·53	43·46	41·51	38·57
Fore-run (g.)	0·750	2·592	2·794	1·990
Nitrodiphenyl in fore-run (%)	3·61	5·98	13·22	16·16
Corrn. nitrodiphenyl (mg.)	27	155	369	322
Corr. wt. of diphenylbenzene–nitrodiphenyl fraction (g.)	3·576	3·944	3·607	3·621
Nitrodiphenyl (%, corr.)	47·90	45·69	47·52	44·03
$^{Ph\cdot NO_2}_{PhPh}K$	1·06	0·97	1·04	0·91
Benzoic acid (g.)	2·23	2·19	2·83	2·38
$(Ph\cdot CO_2)_2$ accounted for (%)	70·1	75·0	76·0	73·6

Mean $^{Ph\cdot NO_2}_{PhPh}K = 1{\cdot}00$.

Determination of the Ratio of Isomerides formed in the Phenylation of Diphenyl.—The standard procedure outlined in Part II (*loc. cit.*) was used for the isolation of the diphenylbenzene fraction from the products of reactions 5 and 6 (see Table 3). In these experiments benzoyl peroxide (6 g.) and diphenyl (150 g.) were used and the reactions were allowed to proceed for 72 hr. in a thermostat at 80°. No high-boiling resin was formed. It was impracticable to determine the composition of the mixtures of the isomeric diphenylbenzenes by the infra-red spectrographic procedure described in Part III (*loc. cit.*) because the *meta*- and the *para*-isomeride had extremely low solubilities in nitromethane, the only suitable solvent. An ultra-violet spectrophotometric method was therefore employed. The instrument used was a Unicam S.P. 500 spectrophotometer.

Calibration spectra of solutions of the three pure isomerides in absolute ethanol were recorded in the wave-length range 220—290 mμ. The concentrations of the solutions employed and the values of the maximum molecular extinction coefficients are given in Table 2. The

TABLE 2.

Compound	Concn., moles/l., $\times 10^5$	Wave-length, mμ ($\lambda_{max.}$)	Max. mol. extinctn. coefficient, $\varepsilon_{max.}$
o-Diphenylbenzene	1·0594	232	27,567
m-Diphenylbenzene	0·9340	248	35,759
p-Diphenylbenzene	0·8579	278	29,723

spectra of the two homogenised experimental mixtures, 5 and 6, were then recorded, the concentrations of the solutions employed being about $1{\cdot}7 \times 10^{-5}$ mole/l. The compositions of the mixtures were calculated by the method outlined below. The results are given in Table 3.

TABLE 3. *Analysis of products obtained in the phenylation of diphenyl.*

Expt.	Composition (%): *ortho*	*meta*	*para*
5	47·0	24·0	29·0
6	50·0	22·0	28·0
Mean	48·5	23·0	28·5

Calculation of the Ratio of Isomerides.—Beer's law, $-\log I_t/I_0 = \varepsilon cd$, is assumed, where I_t and I_0 represent the transmitted and the incident radiation respectively, ε is the molecular extinction coefficient, c is the concentration of the absorbing substance in moles/l., and d is the cell thickness. The cells employed in the determination had $d = 1$ cm. The quantity $-\log I_t/I_0$ is the optical density O. For a mixture of three isomerides *o*-, *m*-, and *p*-, at a fixed wave-length λ,

$$O_{mixt.} = O_o + O_m + O_p$$

or

$$\varepsilon_{mixt.}\, c_{mixt.} d = \varepsilon_o c_o d + \varepsilon_m c_m d + \varepsilon_p c_p d$$

and, since $d = 1$,

$$\varepsilon_{mixt.} = \varepsilon_o x + \varepsilon_m y + \varepsilon_p z \quad \ldots\ldots\ldots \quad (1)$$

where x, y, and z are the fractions of the *o*-, *m*-, and *p*-isomerides, respectively, in the mixture, and ε_o, ε_m, and ε_p are their respective extinction coefficients at the wave-length considered.

Similarly, at another wave-length λ',

$$\varepsilon'_{\text{mixt.}} = \varepsilon'_o x + \varepsilon'_m y + \varepsilon'_p z \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Also

$$x + y + z = 1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Thus, the composition of the mixture may be calculated by solution of the equations (1), (2), and (3), the values of the various extinction coefficients being obtained from the spectra of the mixture and the three pure isomerides. It was found that, whereas all three isomerides absorbed strongly in the region of maximum absorption of *o*-diphenylbenzene, the absorptions due to the other isomerides were relatively small in the regions of maximum absorption of *m*- and *p*-diphenylbenzene. Accordingly, the twelve pairs of wave-lengths λ and λ' at which measurements were made were chosen so that they lay near the absorption peaks of the *meta*- and the *para*-isomeride.

The accuracy of the determination was checked by using equation (1) in conjunction with the determined values of x, y, and z, to calculate $\varepsilon_{\text{mixt.}}$ at a large number of wave-lengths for a mixture of a composition represented by x, y, and z. Comparison of this calculated value with the extinction coefficient as actually determined gave a measure of the accuracy of the analysis at that wave-length. This procedure was carried out at 34 different wave-lengths taken over the whole range, and the percentage error calculated at each wave-length. At the peaks the error was zero, but the determination was less accurate at points of low optical density. From this set of 34 points the arithmetical mean error and the standard deviation from the mean error were calculated. The standard deviation from the mean error (+0·5) for the determination of the composition of mixture 6 was found to be $\pm 2{\cdot}5\%$. The determination of the composition of mixture 5 was equally satisfactory.

Reagents.—Diphenyl (B.D.H.) was dissolved in ethanol, treated with activated charcoal, and recrystallised to constant m. p. (70°) from the same solvent. *o*-Diphenylbenzene was prepared by decomposition of 2-nitrosoacetamidodiphenyl in benzene. 2-Acetamidodiphenyl (8·8 g.), m. p. 120° (from benzene–light petroleum), prepared from 2-aminodiphenyl (B.D.H.), was stirred at 0° with acetic acid (25 ml.), acetic anhydride (25 ml.), fused potassium acetate (5 g.), and phosphoric oxide (0·5 g.), while nitrosyl chloride (3 g.) in acetic anhydride (14 g.) was slowly added. Stirring was continued for 90 min. at 0°. The pale yellow mixture was poured very slowly into cold water (500 ml.) containing sufficient sodium hydrogen carbonate to neutralise the acetic acid. The yellow solid which was precipitated was collected on a cooled filter and washed with cold water (100 ml.). The product rapidly darkened, even in a desiccator at 0°. The entire yield (about 8 g.) was therefore dissolved in benzene (200 ml.), stirred over anhydrous sodium sulphate at room temperature until no more nitrogen was evolved (2 days), and then warmed to 45° for 2 hr. The dark red solution was filtered, the solvent removed under reduced pressure, and the black residue distilled *in vacuo*, yielding an orange solid (4 g.), b. p. 120—130°/0·1 mm., m. p. 94—110°. Recrystallisation from benzene–light petroleum gave 2-acetamidodiphenyl, m. p. and mixed m. p. 119°. The mother-liquors from the recrystallisation were diluted with benzene and extracted repeatedly with concentrated sulphuric acid until both layers were colourless. The benzene solution was washed with alkali and then water (twice) and was evaporated to give *o*-diphenylbenzene (1·0 g.), which was recrystallised to constant m. p. (57°) from methanol.

m- and *p*-Diphenylbenzene (B.D.H.) were decolorised by means of activated charcoal, and recrystallised to constant m. p. from benzene–light petroleum (*m*-diphenylbenzene, colourless prisms, m. p. 85—86°; *p*-diphenylbenzene, colourless plates, m. p. 210°). Benzoyl peroxide (May and Baker) and nitrobenzene (B.D.H. " AnalaR ") were purified according to the procedures described in Part II (*loc. cit.*).

Discussion

The relative rate of substitution in diphenyl, ${}^{\text{PhPh}}_{\text{PhH}}K$, may be calculated from ${}^{\text{PhPh}}_{\text{Ph·NO}_2}K$ and ${}^{\text{Ph·NO}_2}_{\text{PhH}}K$, the determination of which was reported in Part II (*loc. cit.*). In this way, ${}^{\text{PhPh}}_{\text{PhH}}K$ is found to be equal to 4·0, that is, diphenyl is phenylated at almost exactly the same rate as nitrobenzene. By using this value, and the mean values obtained in spectrophoto-

metric analysis for the ratio of isomerides (Table 3), the following values are obtained for the partial rate factors :

$$F_o = 2{\cdot}9;\ F_m = 1{\cdot}4;\ F_p = 3{\cdot}4;$$

since $$^{\mathrm{PhPh}}_{\mathrm{PhH}}K = \tfrac{1}{6}\{4\,^{\mathrm{PhPh}}_{\mathrm{PhH}}F_o + 4\,^{\mathrm{PhPh}}_{\mathrm{PhH}}F_m + 2\,^{\mathrm{PhPh}}_{\mathrm{PhH}}F_p\}$$

and this takes into consideration the fact that there are 4 *ortho*-, 4 *meta*-, and 2 *para*-positions in the diphenyl molecule.

It may be noted that diphenyl conforms to the general pattern of homolytic substitution established in the preceding Parts, in that it is moderately activated towards substitution and that substitution takes place largely in the *ortho*-positions. It is also noteworthy that the sum of the partial rate factors (11·6) for the four *ortho*-positions in diphenyl, which is proportional to the amount of the 2-isomeride produced, is close to the corresponding figure (14·0) for the two *ortho*-positions in nitrobenzene. A similar relationship exists for the *meta*- and the *para*-positions in the two molecules. It appears, therefore, that a phenyl and a nitro-group influence the properties of an aromatic nucleus in homolytic substitution reactions in a similar manner. That this should be so for two groups of such dissimilar polar character, is a striking indication of the insensitivity of homolytic reactions to polar influences.

Calculations have been performed for diphenyl of atom localisation energies for homolytic substitution (Seel, *Z. Elektrochem.*, 1948, **52**, 191; *Z. Naturforsch.*, 1948, **3***a*, 35), and free valence numbers (Burkitt, Coulson, and Longuet-Higgins, *Trans. Faraday Soc.*, 1951, **47**, 553). Both sets of calculations predict qualitatively that the 2- and the 4-positions should be activated towards homolytic attack, the activation being greater in the 2-position, and that the 3-position should be slightly deactivated. This qualitative result is in agreement with the experimental data, except in the case of the 3-position, which has been found to be slightly activated.

The predictions are, however, not borne out in a quantitative sense. The degree of activation predicted by the atom localisation energies is very much too large, and in the case of the free valences the expected relation

$$\log F_r \propto (f_r - f_b),$$

where F_r is the partial rate factor of the rth position of the molecule, f_r is the free valence of that position, and f_b is the free valence of any position in benzene, is not obeyed. Thus, although these calculations are capable of making fairly reliable qualitative predictions of the rate and position of homolytic attack in simple aromatic systems, yet they are at present too crude to be of any quantitative value for this purpose. This crudity may possibly be attributed, in the present instance, to a neglect of overlap integrals in making the calculations. The much greater success of Wheland's calculations (*J. Amer. Chem. Soc.*, 1942, **64**, 900) for nitrobenzene and chlorobenzene (cf. Parts II and III, *locc. cit.*) may be due to the fact that in these calculations overlap integrals were not neglected.

Thanks are accorded to the Department of Scientific and Industrial Research for the award of a maintenance grant to J. I. G. C.

King's College (University of London),
Strand, London, W.C.2.

[*Received, October 22nd,* 1953.]

Cyclisation of Arylbutyric Acids with Polyphosphoric Acid. The By-products.

By R. F. Evans and J. C. Smith.

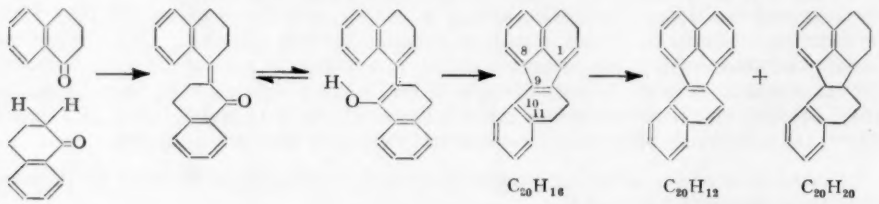
[Reprint Order No. 4777.]

Ring closures of arylbutyric acids may rapidly and advantageously be carried out with polyphosphoric acid at temperatures of 150—170°, but prolonged heating with the reagent converts the resulting tetralones into complex products, in some cases 10 : 11-benzofluoranthenes.

The use of " polyphosphoric acid " (a solution of phosphoric oxide in syrupy phosphoric acid) introduced by Koebner and Robinson (*J.*, 1938, 1995) has become general for ring-closures of aryl-propionic, -butyric, and -valeric acids (Birch, Jaeger, and Robinson, *J.*, 1945, 585; Bachmann and Horton, *J. Amer. Chem. Soc.*, 1947, **69**, 58; Snyder and Werber, *ibid.*, 1950, **72**, 2962, 2965; Gilmore and Horton, *ibid.*, 1951, **73**, 1411; Snyder and Roeske, *ibid.*, 1952, **74**, 5820; Mosby, *ibid.*, p. 2564; Koo, *ibid.*, 1953, **75**, 1891; Evans and Smith, *J. Inst. Petrol.*, 1951, **37**, 80).

In an investigation of the ring-closure of γ-2 : 4-dimethylphenylbutyric acid to 1 : 2 : 3 : 4-tetrahydro-5 : 7-dimethyl-1-oxonaphthalene, Evans and Smith (*loc. cit.*) found that the most satisfactory conditions (considering yield, economy of reagents, and speed of working) were (*a*) use of 1 part of the butyric acid to 10 parts of polyphosphoric acid, (*b*) a temperature between 150° and 170°, and (*c*) a reaction time of 2—3 minutes. Under these conditions the cyclisation of a series of γ-mono- and -di-methylphenylbutyric acids gave 80—93% yields of tetralones. In no case was there detected any migration of the substituents in the aromatic ring (cf. Mosby, *J. Org. Chem.*, 1953, **18**, 485.)

In those ring-closures in which the yields of tetralones had fallen much below 90% it was noticed that if the temperature exceeded 170° or the reaction time 3 minutes (even at 160—170°) rapid formation of by-products resulted. Further, if α-tetralone itself was heated at 170° with polyphosphoric acid, similar oily by-products were formed. From the by-product (b. p. 200°/0·025 mm.) a colourless hydrocarbon, $C_{20}H_{20}$, of m. p. 149° and also a yellow hydrocarbon, $C_{20}H_{12}$, m. p. 163—164° (picrate, m. p. 194—195°), were obtained.



As Nenitzescu and Avram (*J. Amer. Chem. Soc.*, 1950, **72**, 3486) have shown that 10 : 11-benzofluoranthene (obtained from tetralin and phosphoric oxide followed by dehydrogenation, or synthesised by three distinct routes) melts at 165° and yields a picrate of m. p. 195°, the course of the reaction with polyphosphoric acid is probably as shown in the annexed scheme. The ketone initially produced reacts in its enol form, losing water, to give a tetrahydro-10 : 11-benzofluoranthene which then disproportionates to the benzofluoranthene and an octahydro-compound. If this mechanism is correct any methyltetralone with a free 8-position should yield a benzofluoranthene. During the formation (by ring-closure of the arylbutyric acids) of 1 : 2 : 3 : 4-tetrahydro-4 : 7- and -5 : 7-dimethyl-1-oxonaphthalene it was possible to isolate substances regarded as tetramethylbenzofluoranthenes from the by-products. But with 1 : 2 : 3 : 4-tetrahydro-5 : 8-dimethyl-1-oxonaphthalene the cyclisation did not take place, the final by-product being a colourless αβ-unsaturated ketone, $C_{24}H_{26}O$, which did not lose water on further heating with poly-

phosphoric acid. Reduction of the carbonyl group by the Huang-Minlon procedure gave an unsaturated hydrocarbon, $C_{24}H_{28}$.

Experimental

Ring-closures.—**1 : 2 : 3 : 4-***Tetrahydro-***5 : 7-***dimethyl-***1-***oxonaphthalene.* To a solution of phosphoric oxide (240 g.) in phosphoric acid (200 c.c.; *d* 1·75) at 160° (oil-bath) **γ-2 : 4-**dimethylphenylbutyric acid (60 g.) was added. This formed a layer above the " polyphosphoric acid " and, on vigorous stirring of the mixture with a thermometer, the temperature fell to 140° and then rose quickly; at 155° the melt became homogeneous. It was kept for 3 min. at 160° and the hot mixture was then poured into cold water. From the mixture ether extracted a red oil; on distillation there was obtained a main fraction of b. p. 113°/0·25 mm. (49·8 g., 92%) which crystallised immediately. A recrystallised specimen melted at 48·8° (thermometer in the liquid) and at 49—50° (capillary tube). The values in the literature vary from 47° to 50°. In a second experiment, in which the melt was kept for 3 min. at 174°, the yield was only 74%, and a brown syrup remained after distillation of the tetralone.

1 : 2 : 3 : 4-*Tetrahydro-***7-***methyl-***1-***oxonaphthalene.* Heating **γ-***p*-tolylbutyric acid (80 g.) in polyphosphoric acid (phosphoric oxide, 240 g., and phosphoric acid, 267 c.c. of *d* 1·75) for 3 min. at 155° gave 64·7 g. (90% yield) of crystalline tetralone, m. p. 31°.

Similarly γ-phenylbutyric acid during 1—2 min. at 155° gave 80—90% yields, **γ-***p*-tolylvaleric acid during 2·5 min. at 161° an 88% yield, and **γ-2 : 5-**dimethylphenylbutyric acid during 3 min. at 165° gave a 93% yield of the corresponding tetralones.

Action of Polyphosphoric Acid on α-Tetralone.—α-Tetralone (11·6 g.) was stirred with a solution of phosphoric oxide (58 g.) in syrupy phosphoric acid (39 c.c.; *d* 1·75) at 170° for 10 min. After the cooled mixture had been poured into water an ethereal extract of it was washed well with water and with sodium carbonate solution, then dried and distilled. Unchanged tetralone (7 g.) passed over at temperatures below 190°/0·03 mm., followed by 0·7 g. of yellow syrup, b. p. 190—200°/0·03 mm., leaving a high-boiling residue (2 g.). On an alumina column a light petroleum solution of the yellow syrup gave a colourless and also a yellow band. Elution with benzene gave, from the colourless band, **1 : 2 : 3 : 4 : 9 : 12 : 13 : 14-***octahydro-***10 : 11-***benzofluoranthene*, m. p. 145—148° (Found : C, 92·1; H, 7·2. $C_{20}H_{20}$ requires C, 92·2; H, 7·8%). From the other band yellow crystals of m. p. 160—162° were obtained and these, after attempted dehydrogenation (refluxing in *p*-cymene solution for 12 hr. with palladised charcoal), gave yellow crystals (from ethanol), m. p. 164° (Found : C, 95·6; H, 4·7. Calc. for $C_{20}H_{12}$: C, 95·2; H, 4·7%). The picrate, brick-red needles from ethanol, melted at 194—195° (Found : C, 65·1; H, 3·1. Calc. for $C_{20}H_{12},C_6H_3O_7N_3$: C, 64·9; H, 3·1%). Nenitzescu and Avram (*loc. cit.*) give for 10 : 11-benzofluoranthene, m. p. 165°, and for the brick-red picrate, m. p. 195°.

By-products of Cyclisation of Arylbutyric Acids.—(i) *From ring-closure of* **γ-2 : 4-***dimethylphenylbutyric acid.* The brown syrup remaining from the distillation of the tetralone, on being rubbed with ether, gave a solid, m. p. 172—181°, most of which was sparingly soluble in boiling ethanol. After 6 crystallisations from benzene–ethanol it yielded a colourless **3 : 4 : 12 : 13-***tetrahydro-*(?)*-tetramethyl-***10 : 11-***benzofluoranthene*, m. p. 198—199° (Found : C, 92·6; H, 7·6%; *M*, in camphor, 272. $C_{24}H_{24}$ requires C, 92·2; H, 7·8%; *M*, 312). This hydrocarbon (0·3 g.), dehydrogenated for 4 hr. in refluxing *p*-cymene (6 c.c.) with palladised charcoal (0·2 g.), gave orange prisms of (?)*tetramethyl-***10 : 11-***benzofluoranthene*, m. p. 194° (Found : C, 93·0; H, 6·8. $C_{24}H_{20}$ requires C, 93·4; H, 6·6%). The *picrate*, ruby needles from *n*-propanol, was unstable and melted at *ca.* 190° (decomp.; rapid heating) (Found : C, 67·0; H, 4·4; N, 7·7. $C_{30}H_{23}O_7N_3$ requires C, 67·0; H, 4·3; N, 7·8%).

(ii) **γ-***p*-Tolylvaleric acid with polyphosphoric acid at 161° (2·5 min.) gave an 88% yield of the tetralone and a small amount of a high-boiling residue. A benzene solution of this residue, chromatographed on alumina, gave a yellow *hydrocarbon* which, crystallised 4 times from ethanol, melted at 221—222° (Found : C, 90·9; H, 8·8. $C_{24}H_{28}$ requires C, 91·1; H, 8·9%). There was insufficient material for dehydrogenation.

(iii) **γ-2 : 5-**Dimethylphenylbutyric acid on ring-closure gave, besides the 93% yield of tetralone, a small amount of high-boiling residue from which, on crystallisation from ethanol–benzene, a colourless *substance*, m. p. 222·5°, was obtained (Found : C, 87·6; H, 8·0. $C_{24}H_{26}O$ requires C, 87·2; H, 7·9%). This was unsaturated towards dilute permanganate solution; it was recovered unchanged from heating to 160° with polyphosphoric acid; it gave complex derivatives with hydroxylamine hydrochloride and with 2 : 4-dinitrophenylhydrazine. But when heated with hydrazine hydrate and sodium hydroxide in ethylene glycol, for 4 hr. at 160°

and then for 5 hr. at 198°, it yielded a colourless *hydrocarbon*, m. p. 156—158° (Found : C, 91·1 ; H, 9·2. $C_{24}H_{28}$ requires C, 91·1 ; H, 8·9%).

One of us (R. F. E.) is indebted to the Department of Scientific and Industrial Research and also to the Hydrocarbon Research Group of the Institute of Petroleum for maintenance grants.

THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY.] [*Received, November 9th,* 1953.]

Studies in the Steroid Group. Part LXVII. Infra-red Absorption of Disubstituted* cis*Ethylenic Centres.*

By H. B. HENBEST, G. D. MEAKINS, and GEOFFREY W. WOOD.

[Reprint Order No. 4539.]

The spectroscopic examination of steroids containing disubstituted *cis*-double bonds in the various possible positions in rings A, B, and C is reported. The particular importance of the C–H out-of-plane bending region (800—650 cm.$^{-1}$) in the infra-red spectrum for establishing the presence of such groupings is emphasized; the 3000 cm.$^{-1}$ region gives additional information. The data for the 800—650 cm.$^{-1}$ region and for the olefinic stretching region (near 1650 cm.$^{-1}$) can be correlated with the degree of steric strain in the unsaturated bonds. The steroid results are compared with those obtained with some simpler analogues.

THE presence of isolated tri- and tetra-substituted ethylenic groups in steroid nuclei, and in favourable cases their actual positions, can be established by use of infra-red and ultra-violet spectroscopy (Jones, Humphries, Packard, and Dobriner, *J. Amer. Chem. Soc.*, 1950, **72**, 86; Bladon, Fabian, Henbest, Koch, and Wood, *J.*, 1951, 532; Bladon, Henbest, and Wood, *J.*, 1952, 2737). The success of these studies prompted a more detailed investigation of steroids containing nuclear disubstituted olefinic bonds, necessarily *cis* in configuration (for brevity, these will be referred to as " *cis*-bonds ").

It is well known that disubstituted *cis*- and *trans*-olefins absorb in three well-separated regions of the infra-red spectrum, and that related pairs of acyclic hydrocarbons can thus be readily differentiated, especially in the olefinic C–H out-of-plane bending region (1000—650 cm.$^{-1}$) (cf. Sheppard and Simpson, *Quart. Reviews*, 1952, **6**, 1; McMurry and Thornton, *Analyt. Chem.*, 1952, **24**, 318). Although disubstituted *cis*- and *trans*-olefins usually show bands near 700 and 970 cm.$^{-1}$ respectively, detailed assignment of bands for compounds other than simple olefinic hydrocarbons may be rendered difficult by the complexity of the spectra in this region (cf. *inter al.*, Sinclair, McKay, Myers, and Jones, *J. Amer. Chem. Soc.*, 1952, **74**, 2578; Crombie, *J.*, 1952, 2997).

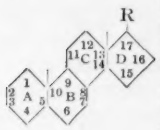
In the cyclic series the spectra of the unsubstituted *cyclo*alkenes containing four- to ten-membered rings have been recorded (*cyclo*butene, Roberts and Sauer, *J. Amer. Chem. Soc.*, 1952, **74**, 3192; *cyclo*pentene, A.P.I., " Catalog of Infra-red Spectral Data," Serial No. 696; *cyclo*hexene, Shreve, Heether, Knight, and Swern, *Analyt. Chem.*, 1951, **23**, 282; A.P.I., *op. cit.*, nos. 201, 697; *cyclo*heptene, Kohlrausch, " Hand- und Jahrbuch der Chemischen Physik," Vol. IX, **6**, 349; *cyclo*octene, Cope and Estes, *J. Amer. Chem. Soc.*, 1950, **72**, 1128; *cis*- and *trans-cyclo*nonene, Blomquist, Liu, and Bohrer, *ibid.*, 1952, **74**, 3643; *cis*- and *trans-cyclo*decene, Blomquist, Burge, and Sucsy, *ibid.*, p. 3636; Prelog, Schenker, and Gunthard, *Helv. Chim. Acta*, 1952, **35**, 1598). Comparison of these results is difficult because the experimental conditions employed vary, and in many cases only a few of the band positions are given. It appears, however, that in the four- and five-membered rings the stretching frequencies are affected in the expected way by steric strain, *i.e.*, raised olefinic C–H and lowered double-bond stretching frequencies.

Jones *et al.* (*loc. cit.*, 1950) have investigated the 3000 and 1650 cm.$^{-1}$ regions of some Δ^{2}- and Δ^{11}-steroids, most of which contained carbon–oxygen bonds as well as the *cis*-

* Part LXVI, *J.*, 1954, 736.

bonds. Apart from this no systematic work appears to have been carried out on fused-ring systems containing *cis*-bonds.

The most obvious application of data from fundamental steroid olefins is for diagnostic purposes in this and related fields. However, since the double bonds are located in rings of different degrees of rigidity, the results should have a wider significance in establishing relations between spectra and molecular environment. A *cis*-bond can be accommodated in five different positions in the six-membered rings A, B, and C. Compounds containing 1 : 2-, 2 : 3-, and 3 : 4-double bonds have been examined as hydrocarbons (cholestenes), whereas the representatives with 6 : 7- and 11 : 12-double bonds have hydroxyl or ester groupings at $C_{(3)}$ and/or $C_{(24)}$; however, these other groups are considered to be sufficiently far removed from the unsaturated centres to cause no appreciable alteration in the spectroscopic properties of the double bond (cf. discussion by Bladon *et al. locc. cit.*, 1951, 1952).



Spectroscopic Work.—The spectra were recorded on a Perkin–Elmer model 21 double-beam spectrometer fitted with a sodium chloride prism. Matched cells were used in order to compensate for solvent absorption. The solutions and path-lengths used were: 3100—2900 cm.$^{-1}$, approx. 0·05M-solutions in carbon tetrachloride, 1-mm. cells; 1800—1600 cm.$^{-1}$, similar solutions in 2-mm. cells; 900—650 cm.$^{-1}$, approx. 0·1M-solutions in carbon disulphide, 0·5-mm. cells. The accuracy of the frequency measurements for sharp bands is estimated as ±10, ±4, and ±2 cm.$^{-1}$ at 3000, 1700, and 800 cm.$^{-1}$ respectively. In the 800—650 cm.$^{-1}$ region the intensities and average frequencies were calculated for the bands listed in the Table by using the expressions:

$$\text{Intensity } (\varepsilon) = \frac{1}{cl}\log_{10}\left(\frac{100-y}{100-x}\right)_{\nu}. \quad \text{Average frequency} = \Sigma\nu(x-y)_{\nu}/\Sigma(x-y)_{\nu}$$

where c = concentration of solution in moles/l., l = path-length in cm., x = % absorption at the frequency ν cm.$^{-1}$ of maximal absorption with solution in the sample beam and solvent in the reference beam, y = % absorption at the same frequency with solvent in both beams. The combined intensities are the sums of the intensities of the separate bands. The main inaccuracy expected in calculations based on % absorption is that no allowance is made for the effect of finite slit width. [The most exact methods circumvent this difficulty by measuring absorption areas rather than peak heights (Ramsay, *J. Amer. Chem. Soc.*, 1952, **74**, 72; Jones, Ramsay, Keir, and Dobriner, *ibid.*, p. 80). These methods require well-separated bands and are difficult to apply to the more crowded 800—650 cm.$^{-1}$ region.] However, under the conditions used in this work (spectral slit width, 2·4—3·3 cm.$^{-1}$, maximal absorption generally 40—70%), errors involved in using % absorption are greatly reduced. The reproducibility of the method was checked by examining cholest-3-ene under differing conditions of background absorption and concentration. Separate determinations gave ε = 235 and 240 for y = 2 and 7% and c = 0·043 and 0·092M, respectively.

The results are tabulated.

Infra-red frequencies (cm.$^{-1}$) of steroids containing disubstituted cis*-double bonds.*

(Sh denotes shoulder on a neighbouring strong band. In the 800—650 cm.$^{-1}$ region figures in parentheses denote intensities.)

	3100—2950	1700—1600	800—650				Combined intensity	Average frequency	Refs.
Δ^1-*Compounds.*									
a Cholest-1-ene *	2995	1644	—	748(65)	718(125) 700(115)	—	305	719	1
b Cholest-1-en-3β-ol	3021	1644	—	751(195)	—	—	195	751	1
c 3β-Acetoxycholest-1-ene	Not measured		—	754(155) 742(60)	—	—	215	750	1
Δ^2-*Compound.*									
d Cholest-2-ene *	3034	1653	774(35)	—	—	664(145)	180	692	—
Δ^3-*Compound.*									
e Cholest-3-ene *	3015	1647	773(110)	—	—	671(125)	235	718	—

TABLE. (*Continued.*)

	3100—2950	1700—1600	800—650				Combined intensity	Average frequency	Refs.
Δ⁶-Compounds.									
f Cholest-6-en-3β-ol	3000	1633	772(70)	739(70)	729(60) 710(60)	—	260	738	2
g 3β-Acetoxycholest-6-ene	3017 Sh	1639	771(90)	739(75)	729(65) 704(60)	—	290	737	2
h 3β-Acetoxycholest-6-en-5α-ol	3014	1638	—	752(175)	—	—	175	752	3
i 3β-Acetoxyergosta-6 : 22-diene-5α : 8α-diol	3010 Sh	1653	—	752(95)	—	—	95	752	4
Δ¹¹-Compounds.									
Methyl 3α-hydroxychol-11-enate	3033	1620	832(85) 794(40)	769(45) 751(50)	725(125)	—	345	771	5
k Methyl 3α-acetoxychol-11-enate	3045	1623	833(75) 796(30)	769(35) 753(45)	726(135)	—	320	770	5
3α : 24-Dihydroxychol-11-ene (mull in Nujol)	3045	1620	830 790	768 748	724	—	—	—	5
m 3α : 24-Diacetoxychol-11-ene	3043	1623	832(70) 796(50)	769(30) 753(55)	724(140)	—	345	768	5
n Methyl 3α : 9α-epoxychol-11-enate	3050	1626	839(55) 800(30) 772(45)	749(115) 739(90)	—	—	335	772	5
o 3β-Acetoxy-5α : 22α-spirost-11-ene	Not measured		831(35) 796(35) 781(30)	766(70) 760(100) 749(40)	703(100)	—	410	760	6
Diene.									
p Cholesta-2 : 6-diene	3020	1646	—	759(275)	694(65)	664(200)	540	709	2
Epidioxides.									
q 2α : 5α-Epidioxycholest-3-ene	3066	†	—	769(65)	711(95) 699(65)	—	225	724	7
r 5α : 8α-Epidioxyergosta-6 : 22-dien-3β-ol	3044 Sh	†	779(55)	—	723(70)	—	125	747	8
s 3β-Acetoxy-5α : 8α-epidioxyergosta-6 : 22-diene	3040 Sh	†	780(45)	—	721(60)	—	105	746	8
3β-Acetoxy-5α : 8α-epidioxyergosta-6 : 9(11) : 22-triene	3019 Sh	†	798(60) 773(25)	741(40)	713(85)	—	210	748	9
Steroids without cis-*bonds.*									
u Cholestane	—	—	799(5)	736(10)	—	—	15	—	—
v Cholestan-3β-ol	—	—	797(10)	732(25)	—	665(25)	60	—	—
w 3β-Acetoxycholestane	—	—	—	732(20)	—	—	‡	—	—
x 3β-Acetoxy-5α : 8α-epidioxyergosta-22-ene	—	—	796(35)	766(15) 738(25)	—	667(20)	95	—	10
Simpler compounds.									
*cyclo*Pentene (A.P.I. data)	3065	1613	—	—	—	—	—	—	—
*cyclo*Hexene	2995	1650	—	—	718(70)	—	70	718	—
3 : 3-Dimethyl*cyclo*hexene	2988	1645	—	—	729(125) 717(65)	—	190	724	11
*cyclo*Hexen-3-ol (liquid film)	3018	1661	—	—	724	668	—	—	—
cis-p-Menth-2-ene-1 : 4-diol	2995	1647	—	772(75)	710(40)	—	115	748	12
Ascaridole	3035	†	—	—	730(50)	695(140)	190	706	—
Acyclic *cis*-olefins	~3020	1660—1630	—	—	730	675	~60	—	13

* Purified *via* dibromides. † Several weak bands in this region.

‡ A broad band at 803 cm.$^{-1}$ (ε = 45), extending to well below 800 cm.$^{-1}$.

1, Henbest and Wilson, forthcoming publication. 2, Barton and Rosenfelder, *J.*, 1949, 2459; Wintersteiner and Moore, *J. Amer. Chem. Soc.*, 1950, **72**, 1923. 3, Henbest and Jones, *J.*, 1948, 1792. 4, Achtermann, *Z. physiol. Chem.*, 1933, **217**, 281. 5, Materials kindly supplied by Dr. K. Folkers and Dr. Max Tishler (cf. Bladon, Henbest, and Wood, *J.*, 1952, 2737). 6, Kindly supplied by Dr. J. Elks (Glaxo Laboratories Ltd.). 7, Kindly supplied by Dr. Werner Bergmann. 8, Windaus and Brunken, *Annalen*, 1928, **460**, 225. 9, Bladon *et al.*, *J.*, 1952, 4883. 10, Clayton, Henbest, and Jones, *J.*, 1953, 2015. 11, Prepared by pyrolysis of the stearate of 2 : 2-dimethyl*cyclo*hexanol by Mr. B. L. Shaw of this Department. 12, Richter and Presting, *Ber.*, 1931, **64**, 878. 13, McMurry and Thornton, *Analyt. Chem.*, 1952, **24**, 318.

The C=C *Stretching Region.*—Isolated double bonds give rise to only low-intensity stretching bands, and when a 1 : 2-disubstituted *trans*-olefin is concerned the vibration may be infra-red inactive (Sheppard and Simpson, *loc. cit.*). Under the conditions employed here more than one band is usually present between 1600 and 1700 cm.$^{-1}$. The strongest band in this region has been taken to be the olefinic stretching frequency; the weaker ones are probably overtones or combination tones of strong bands lower in the spectrum. The values so obtained for compounds *d*, *j*, and *k* agree within experimental error with those recorded by Jones *et al.* (*loc. cit.*, 1950).

As discussed earlier (Bladon *et al.*, *loc. cit.*, 1951), increased steric strain in cyclic olefins would be expected to reduce the double-bond stretching frequency (cf. values for *cyclo*hexene and *cyclo*pentene). In the simplest steroid *cis*-olefins (*a*, *d*, *e*, *f*, and *j*), the frequency order is $\Delta^2 > \Delta^3 > \Delta^1 > \Delta^6 > \Delta^{11}$. This order (with the possible exception of Δ^3 versus Δ^1) is that which could be predicted by consideration of the probable strains. Thus, the Δ^{11}-bond is situated in ring C, the most rigid and strained of the three six-membered rings (*trans*-fused to two other rings, one five-membered; cf. also data on $\Delta^{9(11)}$-steroids, Bladon *et al.*, 1951). The Δ^6-bond is present in the somewhat less rigid ring B, and the remainder are in the relatively flexible ring A. There is much chemical evidence indicating that Δ^2-olefins are more stable than Δ^3-compounds when rings A and B are *trans*-fused (as in the examples studied in this work) [cf. predominance of Δ^2-olefins produced on dehydration of 3-hydroxy-compounds and their derivatives; oxidation (to 2 : 3-*seco*diacids), bromination (at $C_{(2)}$), and enol acetylation (to Δ^2-3-acetates) of 3-ketones of the 5α-series]. Although hyperconjugation (as in conjugated dienes, cf. Barton and Brooks, *J.*, 1951, 257) may play some part in these relative stabilities (4 hydrogen atoms in Δ^2-, and 3 in Δ^3-steroids), strain is likely to be much more important. Thus the direction of oxidation and enol acetylation of 3-ketones is reversed when rings A and B are *cis*-fused (3 : 4-*seco*diacids and Δ^3-3-acetates being produced), while, of course, the number of hydrogen atoms in hyperconjugation with the Δ^2- and Δ^3-bonds is the same as in the A–B-*trans*-compounds. Comparable reactions at $C_{(2)}$ would indicate the relative stabilities of Δ^1- and Δ^2-steroids, but the only pertinent observation is that by Ruzicka, Plattner, and Furrer (*Helv. Chim. Acta*, 1944, **27**, 524) who describe the oxidation of cholestan-2-one to the 2 : 3-*seco*diacid obtained previously from cholestan-3-one. This may be taken as an indication of the superior stability (less strain) of Δ^2- compared with Δ^1-compounds. The infra-red results are thus in line with the chemical evidence.

Steroid epidioxides and ascaridole give a number of rather ill-defined low-intensity bands in this region, and reliable identification of the olefinic stretching bands becomes impossible.

The Olefinic C–H *Out-of-plane Bending Region.*—These deformation frequencies occur in the 1000—650 cm.$^{-1}$ region. The bands associated with *cis*-bonds in acyclic olefins generally appear near 700 cm.$^{-1}$, but their positions are known to be rather variable (Sheppard and Simpson, *loc. cit.*).

In general, steroids containing *cis*-bonds have been found to show several prominent bands in the 800—650 cm.$^{-1}$ region, while the corresponding saturated compounds give only weak bands. The position of the peaks associated with the *cis*-bonds distinguishes them from the bands at 850—790 cm.$^{-1}$ given by the trisubstituted olefins (Bladon *et al.*, *loc. cit.*, 1950) which are often of lower intensity [*e.g.*, cholest-5-ene has bands at 833 ($\varepsilon = 70$) and 800 cm.$^{-1}$ ($\varepsilon = 65$)].

Examination of the compounds in which there is no oxygenated substituent near the *cis*-bond shows that each position of the double bond is associated with a definite absorption pattern. Since the bands within these patterns often have similar intensities it is impossible to assign any particular peak to the out-of-plane vibration. The reason for the multiplicity of bands in most of the compounds studied is not obvious. It may be noted that *cyclo*hexene, the only completely symmetrical olefin, resembles the acyclic compounds in giving only a single band, and it is possible that the " unsymmetrical environment " of the *cis*-bonds in the other compounds is connected with the more complex absorption pattern (the steroid olefins can all be considered as unsymmetrical with respect to the degree of substitution of adjacent atoms and strain differences in the single bonds joined to

the unsaturated centre). (It is possible, of course, that further characteristic bands may be present below 650 cm.$^{-1}$, but in the absence of experimental data this cannot be discussed further.)

In order to help towards an interpretation of the somewhat complex absorption observed in this region, an " average frequency " has been computed for each compound (relative intensities have been taken into account in these calculations; use of ε values instead of % absorption makes little difference to the figures obtained). While the physical significance of this average frequency cannot be assessed until the origin of the multiple absorption is known, use of this quantity leads to a rationalisation of the results. Thus, the average frequencies of the simplest steroid olefins (*a*, *d*, *e*, *f*, and *j*) are in the order previously observed in the double-bond stretching region; these deformation frequencies however, are ***raised*** by increase in strain. (The Δ^{11}-compounds are exceptional in giving significant bands just above 800 cm.$^{-1}$. These are included in the Table as they occur regularly in compounds *j*, *k*, *l*, *m*, and *n*, and thus appear to be members of the Δ^{11}-band group. Even if they are omitted, the average frequencies of the Δ^{11}-steroids are still higher than those of the other types.*)

Individual intensities of the steroid peaks (ε *ca.* 50—150) are of the same order as those of the simpler derivatives of *cyclo*hexene examined. Compared with acyclic *cis*-bonds (ε *ca.* 60) all the *cyclo*hexene compounds (including steroids) tend to give somewhat stronger bands. The values of the band intensities (or combined intensities) of the Δ^{6}- and Δ^{11}-compounds may be influenced by the presence of the oxygenated substituents. Although such groups are not expected to give bands in this region, or to influence the positions of the olefinic peaks (if sufficiently far removed from the *cis*-bond, see below), their presence may enhance the intensity of individual olefinic peaks, or alternatively may increase the general level of absorption (cf. *u*, *v*, *w*, and *x*). However, comparison of the Δ^{1}-, Δ^{2}-, and Δ^{3}-hydrocarbons (*a*, *d*, and *e*) shows that the combined intensity of cholest-1-ene (ε 305) is much greater than those of its two isomers (ε 180 and 235). Possibly the intensities are influenced by the degree of substitution on the two *adjacent* carbon atoms, which is known to be important for ultra-violet absorption intensities of identically substituted olefins (Bladon *et al.*, *loc. cit.*, 1952). The *cis*-bond in cholest-1-ene is linked to the quaternary $C_{(10)}$ and to a methylene group, $C_{(3)}$, and the relatively high intensity of the Δ^{1}-peaks may be due to the dissymmetry of this substitution (dissymetry and combined intensity decrease in the order $\Delta^{1} > \Delta^{3} > \Delta^{2}$). In this connection it may be noted that 3 : 3-dimethyl*cyclo*hexene has a higher intensity than *cyclo*hexene, and that β-amyradiene-II (effectively a 4 : 4-dimethyl-Δ^{2}-steroid) absorbs more strongly (combined ε 285; unpublished work) than cholest-2-ene (ε 180) in the 800—650 cm.$^{-1}$ region.

An increase in the number of functional groups (oxygenated groups in the present study) renders interpretation of the experimental results more difficult. Thus, although variation in the nature of oxygenated groups at positions distant from the *cis*-bond causes little alteration in the spectra (cf. *f* and *g*; *j*, *k*, and *m*), introduction of such groups nearer to the ethylenic bond may profoundly alter the band positions and intensities. For example, the three steroid allylic alcohols (*b*, *h*, and *i*) are exceptional in that each shows only a single band (near 750 cm.$^{-1}$ in each case; however, *cyclo*hexen-3-ol shows a doublet). The combined intensities of these steroid alcohols are less than those of the olefins lacking the hydroxyl group (the intensity decrease is most marked in the doubly allylic diol *i*).

The allylic ether (*n*) has a group of five bands similar to those of the simpler Δ^{11}-compounds and, although the average frequency and combined intensity are near the characteristic Δ^{11}-values, the positions and intensities of the individual bands are considerably altered. These effects also apply to the Δ^{11}-sapogenin (*o*) which shows a group of six bands [sapogenin side-chains do not give appreciable bands in the 800—

* It would clearly be of interest to examine the spectra in the 5β-series, where the frequency order of Δ^{2}- and Δ^{3}-olefins might be the reverse of that in the 5α-series. Through the courtesy of Professor L. F. Fieser we have been able to record the spectrum of one 5β-compound, methyl chol-3-enate (Fieser and Ettorre, *J. Amer. Chem. Soc.*, 1953, **75**, 1700). This gives bands at 783 (weak) and 678 (medium-strong) cm.$^{-1}$ in the 800—650 cm.$^{-1}$ region (there was insufficient compound to give reliable ε values). The average frequency (~693 cm.$^{-1}$) is less than that of cholest-3-ene, in accord with the greater stability of Δ^{3}-compounds in the A–B-*cis*-series.

650 cm.$^{-1}$ region (Jones, Katzenellenbogen, and Dobriner, *J. Amer. Chem. Soc.*, 1953, **75**, 158)]. Introduction of an epidioxide group at the positions adjacent to the *cis*-bond makes detection of the latter more difficult (cf. rather small intensity differences between *s* and *x*). Such groups tend to increase the average frequency of the neighbouring *cis*-bond (Δ^3, 718 ⟶ 724 cm.$^{-1}$; Δ^6, 738 ⟶ 747 cm.$^{-1}$), possibly indicating increased strain.

One unconjugated diene, cholesta-2 : 6-diene (*p*), has been examined, the *cis*-bonds being situated in different but neighbouring rings. Its spectrum differs considerably from those of Δ^2- and Δ^6-compounds, and the combined intensity (ε 540) is appreciably greater than the value obtained (ε ~440) by adding the intensities of the individual *cis*-bonds.

The Olefinic C–H *Stretching Region.*—In many olefins detection of the olefinic-hydrogen stretching bands is made difficult by their proximity to the relatively more intense saturated C–H stretching bands, and a prism of high dispersive power is generally used (*e.g.*, a lithium fluoride prism was used in our previous work on trisubstituted steroid olefins). However, the lower resolution of sodium chloride is now found to be adequate for the detection of *cis*-bonds. Thus steroids and simpler compounds containing a *cis*-bond exhibit a well-defined peak, or, in the more complex steroids, a marked shoulder, in the 3050—3000 cm.$^{-1}$ region. Numerous observations in these laboratories have shown that the steroid *trans*-Δ^{22}-bond gives either a slight shoulder or no inflection in this range (sodium chloride prism). This difference is probably connected with the greater intensity of the *cis*-band, for the two types of system do not appear to absorb at systematically different frequencies. Other examples of *cis*-bonds' giving better defined peaks in this region are found in the spectra of vitamins A_1 and A_2 and related compounds (Farrar, Hamlet, Henbest, and Jones, *J.*, 1952, 1094), and in long-chain unsaturated acids (Sinclair *et al.*, *loc. cit.*, 1952).

More highly strained olefins are usually expected to absorb at higher frequencies in the olefinic C–H stretching region (cf. *cyclo*pentene and *cyclo*hexene). Indeed, the most strained of the steroids, the Δ^{11}-compounds, absorb at greater frequencies than the remainder (with the exception of some of the epidioxides). However, in the other compounds, variation in double-bond environment causes only small frequency changes, which do not conform to any discernible pattern.

From the present work it is clear that the 800—650 cm.$^{-1}$ region is the most useful for detection of *cis*-bonds in six-membered rings. Its value is enhanced by the fact that mono- and poly-cyclic derivatives of *cyclo*hexene without *cis*-bonds do not often absorb strongly in this range, although many bands are present between 1000 and 850 cm.$^{-1}$ (see, *inter al.*, Beckett, Pitzer, and Spitzer, *J. Amer. Chem. Soc.*, 1947, **69**, 2488). The intensities of the bands in the latter region are generally comparable with those observed with the *cis*-bonds at lower frequencies. In the evidence for the presence of a *cis*-bond in soya-sapogenol-C (*cyclo*hexene ring present) (Meyer, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1950, **33**, 672) and clovene (*cyclo*pentene ring present) (Eschenmoser and Günthard, *ibid.*, 1951, **34**, 2338) bands at 970 and 969 cm.$^{-1}$ are listed. From the published spectra these bands appear to be of only moderate intensity, and in both cases far stronger bands are present near 760 cm.$^{-1}$; these are probably more significant for confirmation of the presence of *cis*-bonds (*cyclo*pentene derivatives have not been considered in this work, but see the spectra published by Roberts and Gorham, *J. Amer. Chem. Soc.*, 1952, **74**, 2278).

The authors thank Professor E. R. H. Jones, F.R.S., for his interest and the various gentlemen listed above for gifts of samples. One of us (G. W. W.) was the recipient of a grant from the Department of Industrial and Scientific Research.

THE UNIVERSITY, MANCHESTER, 13. [*Received, July 29th*, 1953.]

The Galactan of Strychnos nux-vomica *Seeds.*

By P. Andrews, L. Hough, and J. K. N. Jones

[Reprint Order No. 4849.]

Strychnos nux-vomica seeds contain a mixture of polysaccharides which, in all, are composed of galactose, mannose, xylose, and arabinose units (roughly 5 : 2 : 1 : 1 w/w). A galactan has been isolated from the seeds: methylation and periodate studies reveal that its structure consists of chains of β-D-galactopyranose units, the majority being linked through $C_{(1)}$ and $C_{(4)}$, but with a small number of branching points arising from units linked through $C_{(1)}$, $C_{(3)}$, and $C_{(6)}$.

The polysaccharide material in *Strychnos nux-vomica* seed is reported (Bourquelot and Laurent, *Compt. rend.*, 1900, **130**, 1411) to consist of galactose and mannose in the proportions 4 : 1. A galactomannan of this composition would be of great interest since, of those examined hitherto, only one contains more galactose than mannose (cf. Andrews, Hough, and Jones, *J.*, 1952, 2744). Further interest arises from the fact that galactomannans have only been isolated from seeds of the family *Leguminosae*, whereas *Strychnos* belongs to the *Loganiaceae*.

The heterogeneity of the polysaccharide material in *Strychnos nux-vomica* seed was shown by the fact that successive extractions of the seed with hot water and with aqueous alkalis gave polysaccharide fractions which differed widely in composition. In addition to galactose and mannose, xylose and arabinose were found, the relative total amounts of the four sugars being roughly 5 : 2 : 1 : 1 w/w respectively. Addition of Fehling's solution to aqueous solutions of the various fractions resulted in complete precipitation of the mannose- and xylose-containing polysaccharides as copper complexes, with partial precipitation of those containing galactose and arabinose. Evidently the seed contains a mixture of polysaccharides which is probably composed of a galactan, a mannan, a xylan, and an araban; neither the galactan nor the araban forms insoluble copper complexes, but is, to some extent, coprecipitated with the insoluble mannan– and xylan–copper complexes. It was not possible to obtain any one polysaccharide in a pure state from some of the fractions isolated from the seed, by fractional precipitation and fractional extraction with aqueous ethanol or fractional precipitation with Fehling's solution. However, small quantities of galactan were isolated from polysaccharide fractions (composed of galactose, mannose, and small amounts of arabinose) which had been freshly precipitated by alcohol, by extracting them with cold Fehling's solution. Some galactan dissolved in this reagent and was recovered from the solution after removal of salts by dialysis and on ion-exchange resins. On hydrolysis the products from each of several experiments yielded, in addition to galactose, small and differing amounts of arabinose (from about 5% to $< 1\%$), depending on the proportions of arabinose in the original polysaccharide mixtures.

The galactan dissolved easily in water; the solution had $[\alpha]_D$ +69° and after seven hours at 100° in N-sulphuric acid hydrolysis was complete, indicating that in the polysaccharide the D-galactose units exist largely in the pyranose form and are joined by β-links. It is interesting that "galactocarolose" (Haworth Raistrick, and Stacey, *Biochem. J.*, 1937, **31**, 640), which is composed of D-galactofuranose units, had $[\alpha]_{5780}$ −84° in water and was hydrolysed in three hours at 100° in 0·01N-sulphuric acid.

The *Strychnos* galactan was methylated by several treatments with methyl sulphate and sodium hydroxide in the usual way to a methoxyl content of 41·6%, but it resisted further methylation (a fully methylated galactan should have a methoxyl content of 45·6%). This material was easily soluble in chloroform and formic acid, but insoluble in acetone, methanol, methyl iodide, or dioxan, solvents which dissolve many methylated polysaccharides. Its optical rotation ($[\alpha]_D$ −6° in chloroform) suggested the presence of a large proportion of β-links. It is noteworthy that Hirst, Jones, and Walder (*J.*, 1947, 1225) observed a similar resistance to methylation by the galactan of *Lupinus albus*.

Since the methylated product was insoluble in methanol, fission to reducing sugars was accomplished by successive treatments with formic acid and N-sulphuric acid. The mono-

saccharide derivatives so produced were identified as 2 : 3 : 4 : 6-tetra-, 2 : 3 : 6-tri-, 2 : 6-di-, and 2 : 4-di-*O*-methyl-D-galactose, in the molecular proportions of about 1 : 24 : 3 : 1 respectively.

The isolation of a di-*O*-methylgalactose fraction suggests that the polysaccharide has a branched chain structure, but a large proportion of this di-*O*-methyl sugar fraction undoubtedly arises from incomplete methylation. Thus, of the two di-*O*-methylgalactoses isolated, the 2 : 4-isomer, but probably not the 2 : 6-isomer, was derived from the galactose units from which the points of branching originate, for the following reasons. (i) Hydrolysis of an incompletely methylated polysaccharide composed of chains of galactose units linked through $C_{(1)}$ and $C_{(4)}$ should yield some 2 : 6(and/or 3 : 6)-di-*O*-methylgalactose, but only the merest trace, if any, of the 2 : 4-isomer, since the latter can only be derived from the non-reducing end groups. The same considerations apply to the products that may be formed by partial demethylation during hydrolysis of such a polysaccharide. (ii) A careful examination of the tri-*O*-methyl-sugar fraction showed that it consisted solely of 2 : 3 : 6-tri-*O*-methyl-D-galactose, and therefore contained no tri-*O*-methyl-sugar which by loss of one methoxy-group (*i.e.*, through demethylation or incomplete methylation) could give 2 : 4-di-*O*-methyl-D-galactose. (iii) The relative molecular proportions of the 2 : 4-di- and the 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactoses were *ca.* 1 : 1, whereas in the case of the 2 : 6-isomer the ratio was *ca.* 3 : 1. Hence, the 2 : 4-isomer probably represents all the points of branching, and the 2 : 6-isomer is an artefact.

The possibility remains that the origin of the 2 : 4-di-*O*-methyl-D-galactose lies in the fact that the sample of galactan used for methylation studies contained a few per cent. of a galactoaraban. However, no arabinose derivatives were detected amongst the hydrolysis products of the methylated galactan, indicating that the methylated arabinose-containing polysaccharide was removed during the fractionation.

About thirty galactose residues (average) per non-reducing end-group are present in the methylated galactan, whereas periodate oxidation of the galactan yielded one molecule of formic acid per seventeen hexose units. These figures indicate (cf. Andrews, Hough, and Jones, *J.*, 1953, 1186) that the galactan has a branched structure, but in the absence of any value for its molecular weight a reliable estimate of the average number of points of branching cannot yet be made.

Clearly, the structure of the *Strychnos nux-vomica* galactan is not yet fully established, but on the basis of the evidence presented above it is suggested that it consists of chains of β-D-galactopyranose units linked in the main through $C_{(1)}$ and $C_{(4)}$, with about 3% of the units existing as non-reducing end groups and a similar proportion of the units linked through $C_{(1)}$, $C_{(3)}$, and $C_{(6)}$, giving the galactan a branched structure. Similarly, the galactan of *Lupinus albus* seeds, investigated by Hirst, Jones, and Walder (*loc. cit.*), consists of 1→4′-linked β-D-galactopyranose units.

Experimental

Chromatography was carried out on Whatman No. 1 filter paper sheets by the descending method (Partridge, *Biochem. J.*, 1948, **42**, 238), with the following solvent systems: (*a*) *n*-butanol–ethanol–water (40 : 11 : 19 v/v), (*b*) *n*-butanol–pyridine–water (10 : 3 : 3 v/v), (*c*) ethyl acetate–acetic acid–formic acid–water (18 : 3 : 1 : 4 v/v). Sugars were detected on the chromatograms with ammoniacal silver nitrate (Partridge, *loc. cit.*) or *p*-anisidine hydrochloride. R_G and R_{Rh} values of sugars and their derivatives are the rates of movement on the paper chromatogram relative to tetra-*O*-methylglucose and to rhamnose respectively, with solvent (*a*) as mobile phase.

Solutions were concentrated under reduced pressure. Optical rotations were determined at 20°.

Preliminary Fractionations.—*Strychnos nux-vomica* seed was provided as a coarse brown powder of which nearly 20% (w/w) was polysaccharide that could be extracted with hot water and a further 8% (w/w) polysaccharide that was soluble in hot aqueous sodium hydroxide. The seed polysaccharides contained galactose, mannose, xylose, and arabinose in roughly 5 : 2 : 1 : 1 proportions.

Fractional extraction of the polysaccharides from the seed (90 g.) with solvents (700 c.c. portions) at 70° gave fractions of widely differing compositions (Table). Fehling's solution (35 c.c. of A; 35 c.c. of B) was added to each extract, and four polysaccharide fractions (I—IV)

were isolated in the usual way (Andrews, Hough, and Jones, *loc. cit.*) from the precipitated copper complexes. The combined mother-liquors from which the copper complexes of fractions I and II were precipitated, were dialysed in Cellophane casing for 48 hr. against tap-water and then poured into alcohol (2 vols.), causing precipitation of further polysaccharide (fraction V). The mother-liquors which had yielded fractions III and IV were similarly treated but yielded very little material.

Fractionation of Strychnos nux-vomica *polysaccharides.*

Fraction	Solvent	Yield (%)	N (%)	Sulphated ash (%)	Composition * Gal.	Mann.	Arab.	Xyl.
I	Water (2 portions)	7	0·2	2·7	2	1	Trace	Trace
II	Water (5 portions)	2	<0·4	2·3	5	1	,,	,,
III	5% NaOH	5·5	<0·3	nil	1	1	*ca.* 5%	,,
IV	20% NaOH	2·5	<0·1	3·0	1	3	Trace	4
V	Water	9	0·9	5·7	3	Nil	1	Nil

* Approximate proportions estimated by relative spot sizes on paper chromatograms (cf. Andrews, Hough, and Jones, *locc. cit.*).

Precipitation and extraction procedures, with ethanol–water mixtures, afforded only a partial fractionation of fraction I and no detectable fractionation of fraction V. Attempts to separate the mannan as its insoluble copper complex from solutions of fractions I and II were likewise unsuccessful, the precipitates containing both galactose and mannose.

Preparation of the Galactan.—Galactan was extracted from fraction II (2 g.), freshly precipitated from its aqueous solution with alcohol, by stirring it in a macerator with Fehling's solution (25 c.c. of A, 25 c.c. of B, 200 c.c. of water) for 5 min. Stirring for longer periods effected no further extraction. The resultant slurry was centrifuged, and the residue (A) was retained; the clear supernatant liquor was neutralised with acetic acid, dialysed to remove most of the salts, and then passed through columns of Amberlite IR-120 and IR-400 ion-exchange resins. The clear, colourless solution so obtained was concentrated to a small volume and poured into absolute ethanol (3 vols.). The precipitated galactan was isolated on the centrifuge, washed successively with absolute ethanol, acetone, and ether, and dried under reduced pressure over silica gel (yield, 0·1 g.). Copper was removed from the material (A) by twice dissolving it in dilute acetic acid (pH 5—6) and precipitating it with alcohol. It was again extracted with Fehling's solution, and the extract, after working up as above, yielded more galactan (0·3 g. from three experiments). A further quantity of purified galactan (*ca.* 1·5 g.) was obtained by the same procedure from a polysaccharide fraction (6 g.), containing galactose and mannose (3 : 1) and a little arabinose (of the order of 2—3%), prepared as were fractions I and II. When this procedure was applied to polysaccharide mixtures composed of galactose, mannose, and higher proportions of arabinose units, the isolated galactan was contaminated with considerable amounts of araban.

Properties and Hydrolysis of the Galactan.—The purified galactan is a white, slightly hygroscopic powder, easily soluble in water to a clear, colourless solution, $[\alpha]_D$ +69° ± 2° (*c*, 1·0 in H_2O) [Found: C, 44·0; H, 6·3; N, 0·3; sulphated ash, 0·5. Calc. for $(C_6H_{10}O_5)_n$: C, 44·4; H, 6·3%].

The rate of hydrolysis of the galactan (110·7 mg.) in N-sulphuric acid (10 c.c.) at 100° was determined by following the change in optical rotation of the solution: $[\alpha]_D$ +68° (initial value) ---► +73° (2 hr.) ---► +78° (4 hr.) ---► +87° (7 hr.) ---► +89° (9 hr.; final value). Estimates of the amount of reducing sugar in the galactan hydrolysate by the alkaline hypoiodite method (Hirst, Hough, and Jones, *J.*, 1949, 928; Chanda, Hirst, Jones, and Percival, *J.*, 1950, 1289) (with 0·1 c.c. of hydrolysate and 2 c.c. of 0·1N-iodine at pH 11·4; oxidation for 3 hr.) gave values of 121·2 and 120·2 mg. (calc. as hexose). Complete hydrolysis of the galactan should give 123·2 mg. of galactose, and $[\alpha]_D$ +89°. D-Galactose was found to have $[\alpha]_D$ +78 ± 2° (*c*, 1·1 in N-H_2SO_4).

The concentrated hydrolysate, after neutralisation in the cold with barium hydroxide and treatment with Amberlite IR-120 ion-exchange resin, showed on the paper chromatogram, besides galactose, traces (1—2%) of arabinose; uronic acids were not detected. D-Galactose, m. p. and mixed m. p. 164—165°, $[\alpha]_D$ +79° (equil. value; *c*, 1·0 in H_2O), was crystallised from the hydrolysate and recrystallised from methanol.

When the galactan was heated at 100° in 0·01N-sulphuric acid for 4 hr., only a trace of galactose was liberated, but several oligosaccharides were detected on the paper chromatogram. Hydrolysis of the galactan was also incomplete after 8 hr. at 100° in 0·1N-sulphuric acid, the solution still containing considerable amounts of oligosaccharides and reducing material of higher molecular weight which remained on the base-line of the paper chromatogram.

The galactan was also hydrolysed to reducing sugars by the commercial enzyme preparation, Pectinol 10M.

Periodate Oxidation of the Galactan.—The galactan was oxidised with potassium metaperiodate (Brown, Halsall, Hirst, and Jones, *J.*, 1948, 27), and the formic acid yield determined. To the galactan (278·3 mg.) in water (20 c.c.) were added potassium chloride (3 g.) and sodium metaperiodate (0·2N; 30 c.c.). The mixture was kept in the dark and occasionally shaken. At intervals, portions (5 c.c.) were withdrawn, ethylene glycol (1 c.c.) was added, and the formic acid titrated with 0·01N-sodium hydroxide (methyl-red screened with methylene-blue) [Found (c.c. of alkali, corr. for blank): 0·76 (70 hr.); 1·03 (174 hr.); 1·02 (239 hr.); 1·00 (282 hr.)]. The titre of 1·03 c.c. of 0·01N-alkali corresponds to the production, from the galactan, of one molecule of formic acid per 17 galactose units.

Methylation of the Galactan.—The galactan (2·5 g.; containing about 5% of araban) was dissolved in 2N-sodium hydroxide (100 c.c.), the mixture cooled in ice, and methyl sulphate (10 c.c.) added dropwise during 1 hr. Then sodium hydroxide (10 g.) and methyl sulphate (12 c.c., dropwise) were again added, followed by twice the quantity of the same reagents. After the reaction was over, the mixture was neutralised with acetic acid and dialysed against tap-water for 48 hr. The resultant clear solution was concentrated to *ca.* 100 c.c., and methylation continued by the alternate addition of sodium hydroxide (40 g.) and methyl sulphate (95 c.c.). After six methylations, with intermediate dialysis and concentration of the mixture, the crude methylated galactan was isolated by filtration of the hot, neutralised reaction mixture. The crude product was somewhat purified by dissolution in chloroform, filtration, and evaporation to dryness, giving a crisp, buff-coloured solid (2·0 g.) (Found: OMe, 39·6; sulphated ash, 4·5%). This material was insoluble in cold and hot water, aqueous sodium hydroxide, acetone, methanol, dioxan, methyl iodide, and liquid ammonia. Attempts to raise its methoxyl content by treatment of small portions with (*a*) sodium hydroxide and methyl sulphate, (*b*) sodium and methyl iodide in liquid ammonia, and (*c*) silver oxide and methyl iodide, were unsuccessful.

The methylated galactan (1·5 g.) was fractionated by boiling it with light petroleum (b. p. 40—60°) and with mixtures of chloroform and light petroleum (b. p. 40—60°) (2 extractions for 30 min. with 30 c.c. of each mixture). The largest fraction so obtained (0·9 g.) {Found: OMe, 41·6; sulphated ash, 2·2%; $[\alpha]_D$ −6° ± 2° (*c*, 1·1 in $CHCl_3$)} was soluble in a 4 : 1 (v/v) mixture, but insoluble in a 7 : 3 mixture. The next largest fraction (0·16 g.) {Found: OMe, 41·5%; $[\alpha]_D$ −4° ± 2° (*c*, 1·1 in $CHCl_3$)} was soluble in a 7 : 3 mixture, but insoluble in a 6 : 4 mixture.

Scission of the Methylated Galactan.—The material was insoluble in methanol, but soluble in anhydrous formic acid, and was therefore hydrolysed as follows: the largest fraction (0·86 g.) was dissolved in formic acid (9 c.c.), water (1 c.c.) was added, and the solution heated at 100° for 3 hr. It was then concentrated, the resultant thin syrup dissolved in N-sulphuric acid (*ca.* 15 mg. of insoluble inorganic material was filtered off), and the solution heated at 100° for 12 hr. It was cooled, neutralised with barium carbonate, filtered, treated with small amounts of Amberlite IR-120 and IR-4B resins, and concentrated to a syrup (0·80 g.) of reducing methyl sugars.

Examination of the Methyl Sugar Mixture.—Paper chromatographic examination of the mixture indicated that it consisted mainly of tri-*O*-methylgalactose (R_G 0·75) which gave a dark-red spot with *p*-anisidine hydrochloride. Small amounts of tetra-*O*-methylgalactose (R_G 0·94) and two di-*O*-methylgalactoses (R_G 0·48, pink-brown spot, and R_G 0·43, dark brown spot) were also present.

The methyl-sugar mixture (640 mg.) was fractionated on a hydrocellulose column (24 × 3 cm.) (Hough, Jones, and Wadman, *J.*, 1949, 2511) with benzene–ethanol mixtures, nearly saturated with water, as the mobile phase. Elution of the sugars was commenced with benzene and ethanol in the proportions 5 : 1, and this was changed in stages to 3 : 1 as the separation proceeded. The following fractions were obtained.

Fraction (1) (29 mg.) was a syrup with n_D^{20} 1·4570 and $[\alpha]_D$ +101° (*c*, 1·0 in H_2O). It consisted mainly of 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose (R_G 0·94), but contained also *ca.* 10% of tri-*O*-methylgalactose (R_G 0·75). When boiled under reflux with aniline (12 mg.) in ethanol (3 c.c.), the fraction yielded *N*-phenyl-D-galactopyranosylamine tetra-*O*-methyl ether (20 mg.), which had m. p. and mixed m. p. 190° and $[\alpha]_D$ +38° (equil. value; *c*, 0·4 in acetone) after recrystallisation from ethanol.

Fraction (2) (510 mg.) [Found: OMe, 42·3. Calc. for tri-*O*-methylhexose, $C_6H_9O_3(OMe)_3$: OMe, 41·8%] was a syrup with $[\alpha]_D$ +90° (*c*, 1·2 in H_2O) which gave only one spot (R_G 0·75) on the paper chromatogram. It was indistinguishable in position and colour reaction (dark-red spot with *p*-anisidine hydrochloride) from 2 : 3 : 6- and 2 : 4 : 6-, but unlike 2 : 3 : 4-tri-*O*-

methylgalactose; the last had R_G 0·71 and gave a much browner spot. Accordingly, a portion of the syrup (300 mg.) was oxidised with bromine water, and the lactone (270 mg.), isolated in the usual way, crystallised spontaneously. This product gave one spot on the paper chromatogram (butanol–ethanol–water solvent, and ammoniacal silver nitrate spray; cf. Abdel-Akher and Smith, *J. Amer. Chem. Soc.*, 1951, **73**, 5859), R_G 1·00, corresponding to 2 : 3 : 6-tri-*O*-methylgalacto-γ-lactone. Under the same conditions, 2 : 4 : 6-tri-*O*-methylgalactolactone gave a long streak on the paper chromatogram, and not a discrete spot.

A portion of the crude lactone was hydrolysed by titration with 0·1N-sodium hydroxide (Found: equiv., 222. Calc. for $C_9H_{16}O_6$: equiv., 220). The sodium salt from 124 mg. of lactone was oxidised with sodium metaperiodate (0·4N; 10 c.c.), and, after oxidation for 3 hr., saturated sodium hydrogen carbonate solution (20 c.c.) was added to the reaction mixture, followed by excess of potassium iodide. The liberated iodine was titrated with 0·1N-sodium thiosulphate (Found: 12·43 c.c. 0·1N-sodium metaperiodate consumed). The result corresponds to the reduction of 1·10 moles of periodate per mole of sodium salt.

The remainder of the crude lactone was recrystallised from ether–light petroleum (b. p. 60—80°) and characterised as 2 : 3 : 6-tri-*O*-methyl-D-galacto-γ-lactone, with m. p. and mixed m. p. 97—98° and $[\alpha]_D$ −38° (init. value; *c*, 1·0 in H_2O) [Found: OMe, 42·1. Calc. for $C_6H_7O_3(OMe)_3$: OMe, 42·3%]. The derived 2 : 3 : 6-tri-*O*-methyl-D-galactonamide was recrystallised from chloroform–light petroleum (b. p. 60—80°), and had m. p. and mixed m. p. 129—130°.

Fraction (3) (65 mg.) [Found: OMe, 29·7. Calc. for di-*O*-methylhexose, $C_6H_{10}O_4(OMe)_2$: OMe, 29·8%] was a syrup, with $[\alpha]_D$ +85° (*c*, 1·1 in H_2O) and R_{Rh} 1·53, which gave a pink-brown spot with *p*-anisidine hydrochloride. On the paper chromatogram, 2 : 4-, 2 : 6-, 3 : 4-, and 4 : 6-di-*O*-methylgalactoses have R_{Rh} values 1·36, 1·53, 1·18, and 1·34 respectively, and show light brown, pink-brown, brown, and dark brown colours with *p*-anisidine hydrochloride.

This fraction crystallised when seeded with the 2 : 6-isomer; recrystallisation from chloroform–light petroleum afforded 2 : 6-di-*O*-methyl-β-D-galactose (27 mg.) as colourless flakes, $[\alpha]_D$ +48° (init. value, *c*, 0·4 in H_2O) ---► +84° (equil. value), m. p. 119—120°, undepressed on admixture with an authentic specimen, m. p. 118° (Dewar and Percival, *J.*, 1947, 1622, give m. p. 119—120°).

Fraction (4) (20 mg.) was a syrup, consisting mainly of a compound indistinguishable from 2 : 4-di-*O*-methylgalactose on the paper chromatogram, but containing also a little of the 2 : 6-isomer. It was induced to crystallise by adding chloroform and scratching the syrup; the crystals (14 mg.) had m. p. 95—96°, raised to 98—99° by recrystallisation from chloroform–light petroleum (yield, 9 mg.), $[\alpha]_D$ +130° (init. value; *c*, 0·3 in H_2O) ---► +85° (equil. value), and $[\alpha]_D$ +50° (init. value; *c*, 0·3 in 2% w/w MeOH–HCl) ---► +80° ± 20° (18 hr.) ---► +90° ±10° (50 hr.) ---► +120° ± 20° (113 hr.) [Found: OMe, 27·7; loss of weight at 100°, 9·1. Calc. for $C_6H_{10}O_4(OMe)_2,H_2O$: OMe, 27·4; H_2O, 8·0%]. Smith (*J.*, 1939, 1724) gives m. p. 103° and $[\alpha]_D$ +122° (10 min.) ---► +86° (equil. value; in H_2O), and Baldwin and Bell (*J.*, 1938, 1461) give m. p. 100—103° for 2 : 4-di-*O*-methyl-α-D-galactose monohydrate. Accordingly, a specimen of 2 : 4-di-*O*-methyl-D-galactose was recrystallised from chloroform–light petroleum, the solution being seeded with the above crystals; the crystals so obtained had m. p. 100—102°, and m. p. 99—101° in admixture with the crystals, m. p. 98—99°.

Quantitative Analysis of the Methyl-sugar Mixture.—The molecular proportions of tetra-, tri-, and di-*O*-methylhexoses were estimated by the alkaline hypoiodite method (Hirst, Hough, and Jones, *loc. cit.*; Chanda *et al.*, *loc. cit.*). The sugar mixture (*ca.* 25 mg.) was separated on the paper chromatogram by using solvent (*c*), and the separated sugars were eluted from the appropriate sections of the papers by Soxhlet-extraction with water (6—8 c.c.). For the estimations, we used 1 c.c. of 0·1N-iodine and 2 c.c. of phosphate buffer (pH 11·4) for the tetra-, double these amounts for the di-, and five times the amounts for the tri-*O*-methylhexoses. The oxidations were allowed to proceed for 3 hr., then 2N-sulphuric acid (vol. equal to that of buffer solution) was added, and the liberated iodine titrated with 0·01N-sodium thiosulphate [Found (results quoted as c.c. of 0·01N-iodine consumed): "tetra," 0·59, 0·41; "tri," 13·26, 10·80; "di," 2·49, 1·80]. These results correspond to tetra : tri : di molecular ratios of 1·0 : 22·5 : 4·2, and 1·0 : 26 : 4·4, corresponding to an average chain length of 30 ± 3 hexose units.

One of us (P. A.) thanks the Directors of Monsanto Chemicals, Ltd., for the award of a Fellowship. We thank Dr. E. J. Shellard for the gift of powdered *Strychnos nux-vomica* seeds.

THE UNIVERSITY, BRISTOL.
[Present address (J. K. N.):
QUEEN'S UNIVERSITY, KINGSTON, ONTARIO.]

[*Received, November 3rd*, 1953.]

Studies in Stereochemical Structure. Part X. Optically Active Desyl Chloride.*

By Robert Roger and Robert Wood.

[Reprint Order No. 4426.]

Although racemisation occurs under most conditions, (+)-desyl chloride is obtained by slow addition of thionyl chloride to (−)-benzoin in pyridine at −40° to −30°.

(−)-Benzoin was first isolated by McKenzie and Wren (*J.*, 1908, **93**, 309) by the action of phenylmagnesium bromide on (−)-mandelamide. This method has remained the principal and easiest for preparation of the optically active benzoins although resolution has been achieved by classical methods (Wilson and Hopper, *J.*, 1928, 2482; Preiswerk and Erlenmeyer, *Helv. Chim. Acta*, 1934, **17**, 329). Furthermore, (±)-mandelic acid is readily resolved by (−)-ephedrine (Roger, *J.*, 1935, 1544).

McKenzie and Wren (*J.*, 1910, **97**, 473) warmed (−)-benzoin with thionyl chloride and obtained completely inactive desyl chloride [confirmed by one of us (R. R.); cf. Preiswerk and Erlenmeyer, *loc. cit.*]. Ward (*J.*, 1929, 1544) improved the preparation of (±)-desyl chloride by adding thionyl chloride to the solid complex formed by heating equimolecular proportions of benzoin and pyridine, but this also gave only the (±)-chloride from (−)-benzoin. Roger and McGregor (*J.*, 1934, 1545), however, found that in the formation of the solid benzoin–pyridine complex optical activity was lost completely. Further attempts at room temperature had no better result. Gerrard has studied the action of thionyl chloride on hydroxylated compounds and the part played by bases in such actions (*J.*, 1939, 99; 1940, 218), and, finally, on consideration of all the data we adopted the following simple procedure: thionyl chloride was added slowly to (−)-benzoin in pyridine at −40° to −30°, and (+)-desyl chloride ($[\alpha]_{5461}$ +168° in acetone) emerged. The yield was not particularly good, some unchanged benzoin being always recovered, and further experiments under differing conditions yielded desyl chlorides of various degrees of optical purity. Table 1 shows the marked effect of temperature and small variations of conditions on the yield and optical purity of the resultant chloride.

Table 1.

Reactants (mols.) [a]			Desyl chloride (recryst.)			Benzoin recovered (recryst.)	
$SOCl_2$	C_5H_5N	Conditions	G.	$[\alpha]_{5461}$ [b]	M. p.	G.	$[\alpha]_{5461}$ [b]
2·5	1	$SOCl_2$ all added at once	1·5	0°	64—64·5°	—	—
1	1·25	$SOCl_2$ added slowly; mixture kept at −60°	0·2	+140	71—72	1·2	−130°
2·5	1	Kept at −30° to −10°.....	0·6	+108	64—75 [c]	0·4	−134
2·5	1	Very slow addn. at −40°	0·62	+168	75—75·5	0·1	−130
2·5	1	Very slow addn. at 0°	0·8	+118·1	68—70	0·4	−115

[a] (−)-Benzoin used = 2 g. (1 mol.). [b] In acetone. [c] Low rotation of (+)-desyl chloride and spread of m. p. indicates a mixed crop of (+)-desyl chloride and (−)-benzoin.

Some rotation dispersions of (+)-desyl chloride are recorded in the Experimental section. For acetone solution this is best expressed by a modified two-term Drude equation,

$$[\alpha]_\lambda = 12{\cdot}42/(\lambda^2 - 0{\cdot}1297) + 27{\cdot}3/\lambda^2$$

in the visible spectrum (see Table 2). Other solvents gave similar results. This offers an interesting comparison with the dispersion of (−)-benzoin in acetone which Roger and McGregor (*loc. cit.*) found was best fitted by a similar type of equation, from which it would seem that the optical character of the fragment Ph·ĊH·COPh is not materially affected by substitution of the more negative Cl for OH.

* Part IX, 1939, 108.

Experimental

Preparation of (+)-Desyl Chloride from (−)-Benzoin.—To a mixture of (−)-benzoin (2 g., 1 mol.; $[\alpha]_{5461}$ −148° in acetone) and pyridine (0·75 c.c., 1 mol.), cooled to between −40° and −30°, thionyl chloride (refluxed with sulphur for some time and then fractionally distilled twice) (1·5 c.c., 2·5 mols.) was added drop by drop with constant shaking : cloudiness developed after about half of the addition. Next day the mixture was cooled to −10° and ice added to decompose the brown solid which had separated overnight. After lixiviation with ether some solid remained undissolved and on recrystallisation from alcohol separated as colourless needles, m. p. 132—133° alone or mixed with authetic (−)-benzoin.

The ether extract was washed with sodium hydrogen carbonate solution, then water, dried (Na_2SO_4), and evaporated. Addition of light petroleum to the residue caused crystallisation of (+)-desyl chloride which, recrystallised from light petroleum, formed colourless needles, m. p. 75—76° [(±)-desyl chloride has m. p. 65—66°], $[\alpha]_{5461}$ +168·4° (*c* 0·618 in acetone) (Found : C, 72·8; H, 4·8; Cl, 15·2. Calc. for $C_{14}H_{11}OCl$: C, 72·9; H, 4·8; Cl, 15·4%). Other rotatory data are given in Table 2.

Table 2. $[\alpha]_D$ *of (+)-desyl chloride* ($l = 2$) *(values calc. from the Drude equation in parentheses).*

			λ (Å)				
Solvent	Concn. (*c*)	Temp.	6234	5893	5780	5461	4358
Acetone	0·4145	16°	118·2° (118·2)	136·3° (135·7)	142·3° (142·5)	165·2° (165·3)	349·7° (350·1)
EtOH	0·453	17·4	122·6	134·7	142·4	167·8	347·7
Dioxan	0·465	18	131·2	139·7	159·2	180·6	365·6
C_6H_6	0·444	16·8	139·6	153·1	171·2	186·9	389·5
$CHCl_3$	0·473	18·6	113·1	126·9	131·1	154·4	323·4
CCl_4	0·421	19·8	71·3	73·6	77·2	87·9	168·7

We thank the Department of Scientific and Industrial Research for a maintenance grant to one of us (R. W.) which has rendered this study possible.

Chemistry Department, University College, Dundee.
University of St. Andrews.

[*Received, June 24th,* 1953.]

Elimination of Water from Glycols. Dehydration of Racemic 1 : 4-Glycols Derived from Acenaphthene.

By Robert Roger and David M. Shepherd.

[Reprint Order No. 4679.]

5-β-Ethoxycarbonylpropionylacenaphthene with methyl- and ethyl-magnesium iodide yields the expected 1 : 4-glycols, which with dilute sulphuric acid or anhydrous copper sulphate give tetrahydrofuran derivatives.

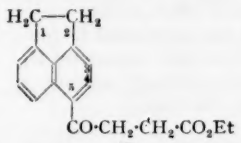
The rearrangement of pinacols and α-glycols occurring on elimination of water has been much studied. In this laboratory the examination of the mechanism of such rearrangements has been facilitated by using optically active substituted hydrobenzoins, and has led to optically active epoxides, diepoxides, ketones, and aldehydes (McKenzie and Roger, *J.*, 1924, **125**, 844, 2148; Roger and McKenzie, *Ber.*, 1929, **62**, 272; Roger and McKay, *J.*, 1933, 332; Roger and Roberts, *J.*, 1937, 1753).

Recently we had occasion to examine the action of Grignard reagents on 5-β-ethoxycarbonylpropionylacenaphthene (I). With methyl- and ethyl-magnesium iodide we obtained the expected 1 : 4-glycols (II; R = Me and Et) respectively.

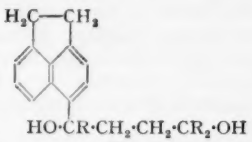
Phenyl-, *cyclo*hexyl-, and α-naphthyl-magnesium bromide yielded only intractable oils; these usually contained some unchanged ester as long heating was avoided.

1 : 4-Glycols have not received the same attention as their α-counterparts. Lieben (*Monatsh.*, 1902, **23**, 60) reviewed the limited data then available and stated that, in general, 1 : 4-glycols yielded tetrahydrofuran derivatives, without intramolecular rearrangement, on treatment with dilute mineral acids. In a recent review of the literature Shepherd (Thesis, St. Andrews, 1951) reports that, of twenty-nine 1 : 4-glycols prepared and dehydrated in the intervening years, twenty-five yielded substituted tetrahydrofurans, and the remaining four gave unsaturated alcohols or diolefins.

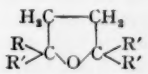
In the present work dehydration of (II; R = Me or Et) by boiling dilute sulphuric acid or a suspension of anhydrous copper sulphate in boiling ethanol gave the tetrahydrofuran derivatives predicted by Lieben's hypothesis, *viz.* (III; R = 3-acenaphthenyl, R′ = Me and Et). Similarly, Kloetzel (*J. Amer. Chem. Soc.*, 1940, **62**, 3045) showed that dehydration of the 5 : 6 : 7 : 8-tetrahydro-1-naphthyl analogue of (II; R = Me) gave the furan derivative (III; R = tetrahydronaphthyl, R′ = Me). The dehydration products (III) possess a centre of asymmetry, and it is hoped in a further communication to deal with the dehydration of optically active 1 : 4-diols.



(I)



(II)


(III)

Experimental

5-β-Carboxypropionylacenaphthene was prepared by the method of Fieser and Peters (*Org. Synth.*, 1940, **20**, 1). Esterification with ethanol–sulphuric acid gave the *ethyl ester* in good yield as needles (from ethanol), m. p. 75—76° (Found: C, 76·8; H, 6·5. $C_{18}H_{18}O_3$ requires C, 76·6; H, 6·4%).

2-5′-Acenaphthenyl-5-methylhexane-2 : 5-diol.—A suspension of the foregoing ester (5 g.) in dry ether (100 ml.) was slowly added, with ice-cooling, to the Grignard reagent prepared from methyl iodide (15 g.). The reaction mass was allowed to reach room temperature, refluxed for 1 hr., and decomposed with ice and dilute sulphuric acid. The product, isolated in the usual way, was a yellow oil (5·3 g.) which was dissolved in hot light petroleum (b. p. 60—80°) containing sufficient ethanol for miscibility. On cooling, a solid separated which, after recrystallisation from the above solvent mixture, gave *2-5′-acenaphthenyl-5-methylhexane-2 : 5-diol* as rectangular prisms (1·6 g.), m. p. 125—126° (Found; C, 80·2; H, 8·5. $C_{19}H_{24}O_2$ requires C, 80·3; H, 8·5%). This glycol gave a blood-red colour with concentrated sulphuric acid.

3-5′-Acenaphthenyl-6-ethyloctane-3 : 6-diol.—A similar reaction (initially at −10°; then at 15° for 72 hr.) gave *3-5′-acenaphthenyl-6-ethyloctane-3 : 6-diol* as rectangular prisms, (2·4 g. from 10 g. of ester), m. p. 112·5—113·5° (Found: C, 81·1; H, 9·2. $C_{22}H_{30}O_2$ requires C, 81·0; H, 9·2%). This also gave a blood-red colour with concentrated sulphuric acid.

2-5′-Acenaphthenyltetrahydro-2 : 5 : 5-trimethylfuran.—(*a*) 2-5′-Acenaphthenyl-5-methylhexane-2 : 5-diol (2 g.) was refluxed for 4 hr. with 20% (vol.) sulphuric acid (25 ml.), then cooled and extracted with ether. The combined extracts were washed with 5% aqueous sodium hydrogen carbonate and then with water. After being dried, the extract yielded a viscous oil which solidified. Recrystallisation from ethanol gave *2-5′-acenaphthenyltetrahydro-2 : 5 : 5-trimethylfuran* as rectangular plates, m. p. 68·5—69° (Found: C, 85·4; H, 8·4. $C_{19}H_{22}O$ requires C, 85·7; H, 8·3%).

The compound gave a brilliant red colour with concentrated sulphuric acid. It did not decolorize bromine in carbon tetrachloride, react with sodium in dry ether, or form a 2 : 4-dinitrophenylhydrazone.

(*b*) The diol (1 g.) was refluxed for 2 hr. with a suspension of freshly prepared anhydrous copper sulphate (2·5 g.) in absolute ethanol (50 ml.). The mixture was then poured into water (200 ml.) and stirred until all the copper sulphate had dissolved; the resulting turbid liquid was extracted with ether. The extract, after being washed with water and dried, gave a viscous oil (0·8 g.) which afforded the tetrahydrofuran derivative, m. p. and mixed m. p. 68·5—69°.

2-5′-Acenaphthenyl-2 : 5 : 5-triethyltetrahydrofuran.—By both methods 3-5′-acenaphthenyl-6-ethyloctane-3 : 6-diol gave *2-5′-acenaphthenyl-2 : 5 : 5-triethyltetrahydrofuran* as rectangular

plates, m. p. 63—64° (Found: C, 85·6; H, 9·2. $C_{22}H_{28}O$ requires C, 85·7; H, 9·1%), its chemical properties being similar to those of the trimethyl analogue.

Attempts to dehydrate these glycols with glacial acetic acid and iodine gave only viscous tars.

We thank the Department of Scientific and Industrial Research for the award of a maintenance allowance to one of us (D. M. S.).

UNIVERSITY COLLEGE, DUNDEE,
UNIVERSITY OF ST. ANDREWS. [*Received, September 25th,* 1953.]

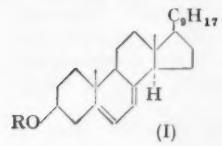
The Isomerisation of Unsaturated Steroids in Liquid Sulphur Dioxide.

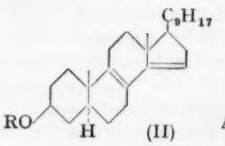
By A. W. D. HUDGELL, J. H. TURNBULL, and WALTER WILSON.

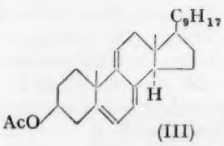
[Reprint Order No. 4790.]

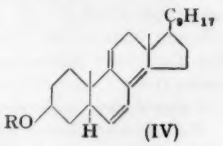
Migration of double bonds in unsaturated steroids often occurs under the influence of liquid sulphur dioxide. Ergosterol and ergosterol D (preferably as acetates) both rearrange to give high yields of pure ergosterol B_1, which thus becomes readily accessible. 5 : 6-Dihydroergosteryl acetate in liquid sulphur dioxide affords 3β-acetoxyergosta-8(14) : 22-diene.

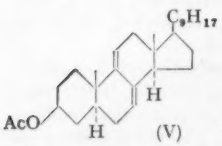
DURING unsuccessful attempts to prepare an adduct from ergosterol (I; R = H) and (liquid) sulphur dioxide, complete rearrangement to ergosterol B_1 (II; R = H) occurred. The effect of liquid sulphur dioxide on other unsaturated steroids was therefore studied. Whilst these experiments were in progress, De Vries and Backer (*Rec. Trav. chim.*, 1952, **71**, 719) reported experiments on the action of sulphur dioxide in ether or ergosterol; they obtained a mixture of isomers, in which only ergosterol B_3 was characterised. No sulphur dioxide adduct was obtained. In a recent preliminary communication, the isomerisation in liquid sulphur dioxide of 9(11)-dehydroergosterol (III) into the 6 : 8(14) : 9(11) : 22-tetraene (IV) is described (Laubach, Schreiber, Agnello, Lightfoot, and Brunings, *J. Amer. Chem. Soc.*, 1953, **75**, 1514).

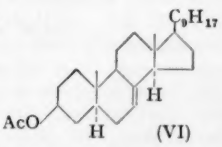

(I)

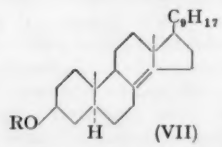

(II)

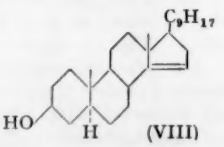

(III)


(IV)


(V)


(VI)


(VII)


(VIII)

In our experiments (Table 1), steroids (usually the acetates) and liquid sulphur dioxide were sealed in Carius tubes, without rigorous exclusion of moisture, and left for several hours at a suitable temperature. Under these conditions, isolated double bonds in the side-chain or at the 5 : 6-position are stable, 7 : 8-double bonds migrate to the 8 : 14-position, and 5 : 7- and 7 : 9(11)-dienes are both isomerised giving the 8(9) : 14-diene system.

Ergosteryl B_1 acetate (II; R = Ac) was obtained in 86% yield from ergosteryl acetate (I; R = Ac), or from ergosteryl D acetate (V). Some specimens of ergosterol B_1 described in the literature are probably impure. The structure of our product has been confirmed independently by Professor D. H. R. Barton (personal communication).

5 : 6-Dihydroergosteryl acetate (VI) was isomerised to 3β-acetoxyergosta-8(14) : 22-diene (VII; R = Ac); molecular-rotation values (Table 2) for the product agree well

with those computed from the data of Barton, Cox, and Holness (*J.*, 1949, 1773). The presence of a tetra-substituted 8(14)-double bond is confirmed by the nature of the absorption near 200 mμ (Bladon, Henbest, and Wood, *J.*, 1952, 2737); trisubstituted double

TABLE 1. *Rearrangement of unsaturated steroids in liquid sulphur dioxide.*

Steroid [1]	Conditions	Product	Yield (%)
5 : 6-Dihydroergosteryl acetate (VI)	100°/18 hr.	3β-Acetoxyergosta-8(14) : 22-diene (VII; R = Ac)	50
Ergosterol (I; R = H)	100°/18 hr.	Ergosta-8(9) : 14 : 22-trien-3β-ol (ergosterol B_1) (II; R = H)	60
Ergosteryl acetate (I; R = Ac)	100°/18 hr.	3β-Acetoxyergosta-8(9) : 14 : 22-triene (II; R = Ac)	86
3β-Acetoxyergosta-7 : 9 : 22-triene (ergosteryl D acetate) (V)	24°/18 hr.	3β-Acetoxyergosta-8(9) : 14 : 22-triene (II; R = Ac)	67
9(11)-Dehydroergosteryl acetate (III)	20°/18 hr.	Sterol (unidentified)	11

[1] Under similar conditions, the following steroids were recovered (80—100%) unchanged: cholesterol, cholesteryl acetate, stigmasteryl acetate, fucosteryl acetate. Gums were obtained from 7-dehydrocholesteryl acetate and benzoate, zymosterol, zymosteryl acetate, and calciferol.

TABLE 2. *Molecular rotations.*

	Sterol	Acetate	Benzoate
Ergosta-8(14) : 22-dien-3β-ol (VII) (calc.) [1]	−59°	− 99°	−103°
Ergosta-14 : 22-dien-3β-ol (VIII) (calc.) [1]	−15	− 45	+ 13
" β "-Dihydroergosterol [2]	−36	− 75	− 40
5 : 6-Dihydroergosterol [3] (VI)	−76	− 88	− 50
Ergosta-8(14) : 22-dien-3β-ol [4] (VII)	−64	−101	− 95

[1] Calc. from figures given by Barton, Cox, and Holness (*loc. cit.*), allowing +103° for the reduction of a 22 : 23-double bond. [2] Barton, Cox, and Holness, *loc. cit.* [3] Barton and Cox, *J.*, 1948, 1354. [4] Present work.

bonds appear to be absent (no characteristic absorption bands in the 3000—3100 $cm.^{-1}$ region). Ergosta-8(14) : 22-dien-3β-ol had not been obtained previously (cf. Barton, Cox, and Holness, *loc. cit.*; Fieser, Rosen, and Fieser, *J. Amer. Chem. Soc.*, 1952, **74**, 5397). Since the completion of our work, Laubach and Brunings (*J. Amer. Chem. Soc.*, 1952, **74**, 705) obtained 3β-acetoxyergosta-8(14) : 22-diene by mild hydrogenation of ergosteryl B_2 acetate, and Nes and Mosettig (*J. Org. Chem.*, 1953, **18**, 276) have isomerised 5 : 6-dihydroergosterol to ergosta-8(14) : 22-dien-3β-ol over copper–chromium oxide.

Liquid sulphur dioxide converted several unsaturated steroids into non-crystalline, sulphur-free products. In the case of zymosterol, mixtures of $C_{(8)}$- or $C_{(9)}$-epimers could be formed when the double bond migrates. 9(11)-Dehydroergosteryl acetate gave a syrup; after hydrolysis, this gave a small yield of an unidentified crystalline sterol: this had twin absorption maxima at 271 and 281 mμ, suggesting the possible presence of a 5 : 7-diene system. There was no evidence for the formation, under the conditions used, of the 6 : 8(14) : 9(11) : 22-tetraene (IV) (Laubach *et al.*, *loc. cit.*) or of the remarkable hydroanthracene derivative obtained by Nes and Mosettig (*J. Amer. Chem. Soc.*, 1953, **75**, 2787) from dehydroergosterol and hydrogen chloride.

In the rearrangement of ergosteryl acetate in liquid sulphur dioxide, the results were less satisfactory when moisture was rigorously excluded. It is believed the isomerisations are initiated by protons produced in the H_2O–SO_2 system. The use of liquid sulphur dioxide is often advantageous instead of the customary reagents for isomerising unsaturated steroids (*e.g.*, hydrogen chloride in chloroform or hydrogenation catalysts; see Fieser and Fieser, " Natural Products Related to Phenanthrene," Reinhold Publ. Corpn., New York, 1949, pp. 240, 255). In particular pure ergosterol B_1 and ergosta-8(14) : 22-dien-3β-ol now become readily accessible.

EXPERIMENTAL

$[\alpha]_D$ are in $CHCl_3$.

Isomerisation of Ergosteryl Acetate.—The acetate (5·0 g.), in a dry Carius tube, was cooled to −60°, and commercial liquid sulphur dioxide (25 c.c.) was added; no precautions were taken to prevent access of moisture. The tube was sealed and heated at 100° (water-bath) for 18 hr.

The tube was cooled, the sulphur dioxide evaporated in a stream of nitrogen, and the orange-brown crystalline residue triturated with methanol. The product, m. p. 131—133°, was recrystallised from ethanol, giving ergosteryl B_1 acetate (86%), m. p. 137—138·5°, $[\alpha]_D$ −50°, $\lambda_{max.}$ 250 mμ (ε 18,000) (Found: C, 82·05; H, 10·45. Calc. for $C_{30}H_{46}O_2$: C, 82·1; H, 10·6%), giving the sterol, m. p. 134—136·5°, $[\alpha]_D$ −41°, both unchanged by chromatography on alumina. Fieser, Rosen, and Fieser (*loc. cit.*) record: ergosterol B_1, m. p. 144—145°, $[\alpha]_D$ −47°; acetate, m. p. 143—144°, $[\alpha]_D$ −60°, $\lambda_{max.}$ 250 mμ (ε 12,300); this low ε value indicates that their material was not quite pure (Barton and Brooks, *J.*, 1951, 257, give $\lambda_{max.}$ 248 mμ, ε 19,800, for dehydro-" α "-ergostenyl acetate which has the same chromophoric system).

Similar experiments (see Table 1) gave the following products.

3β-Acetoxyergosta-8(14): 22-diene (isolated by chromatography and recrystallised from ethanol), m. p. 131—132°, $[\alpha]_D$ −19·6°, $\lambda_{max.}$ 210 mμ (ε 7400) (Found: C, 82·1; H, 10·9. Calc. for $C_{30}H_{48}O_2$: C, 81·75; H, 11·0%), giving the sterol, m. p. 145—148°, $[\alpha]_D$ −15°, and the *benzoate*, m. p. 134—135°, $[\alpha]_D$ −19° (Found: C, 83·6; H, 10·05. $C_{35}H_{50}O_2$ requires C, 83·6; H, 10·3%). Nes and Mosettig (*J. Org. Chem.*, 1953, **18**, 276) give: sterol, m. p. 129—130°, $[\alpha]_D$ −14°; acetate, m. p. 120—122°, $[\alpha]_D$ −24°. Laubach and Brunings (*loc. cit.*) report for the acetate m. p. 122·6—124°, $[\alpha]_D$ −26·5°. These m. p.s are appreciably lower than those observed in the present experiments.

Ergosta-8(9): 14: 22-trien-3β-ol (crystallised from ethanol), m. p. 139—140°, $[\alpha]_D$ −42° (Found: C, 81·7; H, 11·2. Calc. for $C_{28}H_{44}O,C_2H_5{\cdot}OH$: C, 81·4; H, 11·4%), giving an acetate, m. p. 135·5—136°, $[\alpha]_D$ −46°, $\lambda_{max.}$ 250 mμ (ε 18,000).

3β-Acetoxyergosta-8(9): 14: 22-triene (crystallised from ethanol), m. p. 132—133°, $[\alpha]_D$ −56°, $\lambda_{max.}$ 249 mμ (ε 18,000), from ergosteryl D acetate.

Unidentified *sterol* (isolated in the last experiment of the Table by alkaline hydrolysis and then chromatography), m. p. 122·5—123°, $[\alpha]_D$ −23°, $\lambda_{max.}$ 271 (ε 8800) and 281 mμ (ε 8400) (Found: C, 82·55; H, 10·4. $C_{30}H_{44}O_2$ requires C, 82·5; H, 10·2%); it gives no adduct with maleic anhydride in boiling benzene.

The authors are grateful to Professor M. Stacey, F.R.S., for encouragement and guidance, and thank the Distillers Company Ltd. for support, Glaxo Laboratories Ltd. for a gift of ergosterol, and Professor D. H. R. Barton for details of unpublished experiments.

CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15.

Received, November 12th, 1953.]

---

*Derivatives of Acetoacetic Acid. Part I. The Reaction of Diketen with 1: 2- and 1: 3-Ketols to give γ- and δ-Lactones.**

By R. N. LACEY.

[Reprint Order No. 4544.]

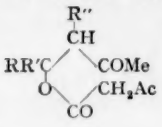
Diketen reacted with diacetone alcohol to give the expected acetoacetate, which, with alkali, readily cyclised to a δ-lactone. β-Hydroxy-αα-dimethylpropaldehyde and β-hydroxy-αγ-dimethylvaleraldehyde reacted with diketen in boiling toluene in the presence of a tertiary amine to give δ-lactones directly, and salicylaldehyde and *o*-hydroxyacetophenone afforded the expected coumarins. Acyloins were converted into γ-lactones by reaction with diketen. In some of the these reactions diketen could be replaced by an acetoacetic ester, but the yields were somewhat poorer.

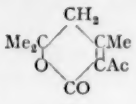
OUR extensive knowledge of the chemistry of acetoacetic esters is mostly concerned with the reactivity of the acetoacetic acid residue itself. Thus, alkylation, acylation, condensation, hydrolysis, etc., are, to a large extent, independent of the parent alcohol, which may find an explanation in the fact that all acetoacetic esters, on dilution with solvents, tend to enolise to the same extent (cf. Henecka, " Chemie der Beta-dicarbonylverbindungen," Springer-Verlag, 1950, p. 11). Nevertheless, it was considered of interest to study the chemistry of derivatives of acetoacetic acid with alcohols, and, subsequently, amines,

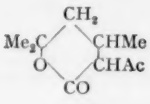
* Patents pending: B.P. Appln. 14581/1951; 10829/1952.

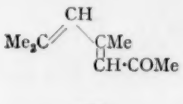
possessing a second functional group which might be induced to react with the acetoacetic acid residue. While many alkyl acetoacetates may be prepared by Claisen condensation or ester exchange, these methods become impracticable when applied to many complex alcohols. However, the use of diketen made available a wide range of acetoacetic esters and amides. The reaction of diketen with simple alcohols is known to be catalysed by acids (Boese, U.S.P. 2,167,168/1939) and by bases such as sodium alkoxide (Chick and Wilsmore, *J.*, 1908, **946**) and tertiary amines (Pohl and Schmidt, U.S.P. 2,351,366/1944). The present paper deals with the reaction of diketen with alcohols (or phenols) possessing a keto or aldehyde group, and with the properties of the products.

Diacetone alcohol reacted smoothly with diketen at 80—90° in the presence of triethylamine to give an 85% yield of the acetoacetate (I; R = R′ = Me, R″ = H), previously obtained by Bader, Cummings, and Vogel (*J. Amer. Chem. Soc.*, 1951, **73**, 4195) in only 4% yield by prolonged ester exchange. This ester cyclised very rapidly with alkali at room temperature, giving a solid, $C_{10}H_{14}O_3$, m. p. 48°, in high yield (first observed by Mr. R. E. Graham). The ultra-violet absorption was characteristic of an αβ-unsaturated ketone, strongly suggesting the unsaturated δ-lactone (II).


(I)

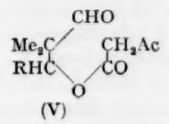

(II)

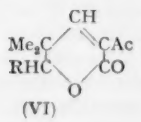

(III)

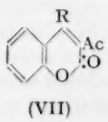

(IV)

Confirmation was provided by hydrogenation, since, on absorption of one mol. of hydrogen, a solid (III) was obtained, which gave a bright violet colour with ferric chloride, characteristic of an α-substituted acetoacetic ester. Alkaline hydrolysis of (II) gave mesityl oxide and 4 : 6-dimethylhepta-3 : 5-dien-2-one (IV) (semicarbazone), although the ultra-violet spectrum indicated that there was also some 4 : 6-dimethylhepta-3 : 6-dien-2-one present. The lactone (II) was also decarboxylated to (IV) by toluene-*p*-sulphonic acid at 100°, recalling the conversion of *tert.*-butyl acetoacetates into ketones, *iso*butene, and carbon dioxide under similar conditions (Renfrow and Walker, *J. Amer. Chem. Soc.*, 1948, **70**, 3957).

Since aldols dehydrate readily to give unsaturated aldehydes (Owen, *Ann. Reports*, 1944, **41**, 146), it was not surprising that diketen and freshly distilled acetaldol, in the presence of triethylamine, gave only crotonaldehyde, acetone, and resinous products. β-Hydroxy-αα-dimethylpropaldehyde with diketen in the presence of triethylamine at 55—65° gave a mixture of the acetoacetate (V; R = H) and the lactone (VI; R = H), but in boiling toluene water was eliminated, and a 75% yield of the lactone (VI; R = H) resulted. The ultra-violet absorption was characteristic of an αβ-unsaturated ketone. Similarly, *iso*butaldehyde aldol diketen gave the unsaturated lactone (VI; R = Pr^i) in 77·5% yield.


(V)

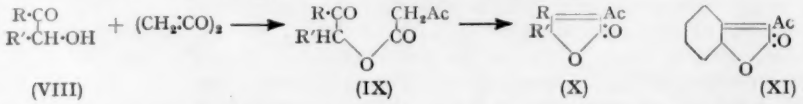

(VI)


(VII)

Among aromatic compounds, salicylaldehyde reacted with diketen in boiling toluene in the presence of triethylamine to give a 45% yield of 3-acetylcoumarin (VII; R = H) although a considerable amount of salicylaldehyde was recovered; *o*-hydroxyacetophenone gave 3-acetyl-4-methylcoumarin (VII; R = Me) in 29% yield.

This direct formation of lactones prompted an attempt to prepare (II) under the same conditions, but the ester (I; R = R′ = Me, R″ = H) failed to cyclise. 4-Hydroxybutan-2-one readily reacted with diketen to give the acetoacetate (I; R = R′ = R″ = H), but this ester was unaffected by refluxing toluene in the presence of piperidinium acetate, and treatment with alcoholic alkali at low temperature gave only low-boiling

products. Similarly, 4-hydroxy-3-methylpentan-2-one, possessing a secondary hydroxyl, gave an acetoacetate (I; R = R'' = Me, R' = H) which also failed to cyclise. The ability of the ester (I; R = R' = Me, R'' = H) to give a lactone on treatment with aqueous or alcoholic alkali seems attributable to the much lower hydrolysis or alcoholysis rate of *tert.*-alkyl esters, the esters of primary or secondary 1 : 3-keto-alcohols being hydrolysed rather than cyclised. With 1 : 3-hydroxy-aldehydes, cyclisation of the acetoacetates occurred even on heating them in the presence of triethylamine, owing to the much greater readiness of aldehydes to undergo the Knoevenagel condensation.



(VIII) (IX) (X) (XI)

The reaction with 1 : 2-hydroxy-ketones was also investigated. Butyroin (VIII; R = R' = Pr^n) in benzene at 60—70° reacted with diketen in the presence of triethylamine to give a mixture, but from the higher-boiling fractions was isolated an oil which analysis showed to be formed by elimination of water from one mole of diketen and one mole of butyroin. The ultra-violet spectrum supported the formulation as an unsaturated γ-lactone (X; R = R' = Pr^n). However, since the product exhibited a purple colour with ferric chloride solution and slowly dissolved in aqueous sodium hydroxide, the prototropic rearrangement to a βγ-unsaturated ketone with an enolisable hydrogen must readily take place.

It therefore appeared that the acetoacetate (IX; R = R' = Pr^n) first formed was partly converted into the lactone. Under more vigorous reaction conditions, *i.e.*, in boiling toluene with provision for the continuous removal of the water eliminated, the lactone was obtained in 80% yield. Again, (VIII; R = R' = Et) reacted in boiling toluene with diketen to give an 84·5% yield of the lactone (X; R = R' = Et). The ultra-violet spectrum indicated an αβ-unsaturated ketone although the lactone gave a purple colour with ferric chloride and slowly dissolved in aqueous alkali. Acetoin reacted similarly but the somewhat lower yield (68·5%) of lactone (X; R = R' = Me) is probably attributable to the lower boiling point and water miscibility of the acyloin, which rendered the water-entrainment procedure less effective. On prolonged storage or after a short period of heating in alcoholic sodium acetate, this lactone gave a solid which appeared to be a dimer containing one carbonyl group.

In the reaction of lauroin (VIII; R = R' = $C_{11}H_{23}$) the calculated quantity of water was eliminated, but the product resisted attempts at distillation and failed to give solid ketonic derivatives. With alkali a solid sodium salt slowly separated and reactions to be described in the next paper indicated that the product must have contained considerable quantities of the expected lactone (X; R = R' = $C_{11}H_{23}$). 2-Hydroxy*cyclo*hexanone with diketen in boiling benzene in the presence of triethylamine gave the expected lactone (XI) in 34% yield.

The reaction of benzoin was similar to those encountered with aliphatic acyloins, for, while reaction at 60—70° gave a mixture, reaction in boiling toluene resulted in the elimination of water and an almost quantitative yield of the expected lactone (X; R = R' = Ph). The product exhibited anomalous ultra-violet absorption at 3550 Å, but since the lactone was subsequently found to form a peroxide very readily in air, this may well account for the enhanced absorption (cf. Waters, *Ann. Reports*, 1945, **42**, 135).

Phenacyl alcohol (VIII; R = Ph, R' = H) reacted with diketen, giving phenacyl acetoacetate, which in refluxing toluene, in the presence of pyridine, lost water giving the lactone (X; R = Ph, R' = H). Phenacyl acetoacetate dissolved in aqueous alkali, and after a few minutes the sodium salt of (X; R = Ph, R' = H) was precipitated: acidification afforded the lactone which gave a weak red colour with ferric chloride and dissolved slowly in dilute aqueous alkali.

Acetol (VIII; R = Me, R' = H) reacted with diketen at 60—70° in the presence of triethylamine to give the acetoacetate. However, although refluxing toluene in the presence of pyridine appeared to have cyclised the ester, with elimination of water, the

product resinified on attempted distillation. Treatment with cold alcoholic alkali gave rise to low-boiling products only.

Since diketen and salicylaldehyde gave 3-acetylcoumarin, a product previously obtained by Knoevenagel (*Ber.*, 1898, **31**, 732) from acetoacetic ester and salicylaldehyde, attempts were made to condense other ketols with acetoacetic ester. The catalysts employed were pyridine, piperidine, triethylamine, or their acetates, the last being generally preferable, since they permitted a higher concentration of catalyst in the boiling reaction mixture. It is probable that with the reactions involving diketen, the true catalyst was the amine acetate, since the diketen employed always contained a few units per cent. of acetic acid. It was found that by refluxing a mixture of methyl acetoacetate and toluene or xylene plus amine or amine acetate catalyst, several of the ketols previously mentioned, *e.g.*, butyroin (67·5% yield), benzoin (56% yield), and *iso*butaldehyde (57% yield), could be converted into the γ- or δ-lactones, although the yields were inferior to those obtained by using diketen.

A useful route to 1 : 2-ketols (type VIII) is the mercuric ion-catalysed hydration of acetylenic alcohols. The hydration of an alkynyl acetoacetate, followed by conversion of the ketol acetoacetate so obtained into a γ-lactone, was therfore attempted. 1-Methylprop-2-ynyl acetoacetate readily prepared by using diketen, was refluxed with mercuric chloride in aqueous ethanol, a 36% yield of the acetoacetate of acetoin being obtained. This was converted into the lactone (X; R = R′ = Me) by refluxing it in toluene containing 2—3% of piperidine.

With the exception of (X; R = Ph, R′ = H), which rapidly decolorised 2 : 6-dichlorophenolindophenol solution, the colour reactions of the lactones tested, with sodium nitroprusside and with 2 : 6-dichlorophenolindophenol (Kuehl, Linstead, and Orkin, *J.*, 1950, 2213), were in agreement with formulation as αβ-unsaturated lactones.

In view of the bacteriostatic properties of certain αβ-unsaturated ketones (cf. Haynes, *Quart. Reviews*, 1948, **2**, 46), the physiological properties of the lactones described may prove of interest.

Experimental

M. p.s were determined on a Kofler block and are corrected. Light-absorption determinations were carried out in ethanol.

Commercial diketen was purified by fractional distillation giving a fraction, 95—98% pure, having b. p. 57—59°/60 mm., n_D^{20} 1·4352—1·4370.

1 : 1-*Dimethyl*-3-*oxobutyl Acetoacetate*.—Diketen (85 g.) was added dropwise to an agitated mixture of diacetone alcohol (116 g.) and triethylamine (0·5 c.c.) at 80—90° during 20 min. Distillation afforded the acetoacetate (I; R = R′ = Me, R″ = H) (170 g., 85%), b. p. 78—83°/0·5 mm., n_D^{20} 1·4425 (Found: C, 60·3; H, 8·4. Calc. for $C_{10}H_{16}O_4$: C, 60·0; H, 8·05%). Bader *et al.*, *loc. cit.*, give b. p. 125—127°/10 mm., n_D^{25} 1·4424.

3-*Acetyl*-5 : 6-*dihydro*-4 : 6 : 6-*trimethyl*-1 : 2-*pyran*-2-*one* (II).—The above acetoacetate (50 g.) was added during 0·5 hr. to alcoholic potassium hydroxide (0·5N; 50 c.c.) with agitation, the temperature being kept below 25°. After a further 0·5 hr., the product was neutralised with acetic acid, concentrated, poured into water, and isolated with ether. Crystallisation of the product (42 g., 92%) from ether–light petroleum (b. p. 40—60°) gave the *pyrone* as prisms, m. p. 48° (Found: C, 66·15; H, 7·65. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·75%). Light absorption: max., 2200 A.; ε, 8000. The *semicarbazone* crystallised from *iso*propanol as prisms, m. p. 204° (decomp.) (Found: C, 55·5; H, 7·3; N, 17·7. $C_{11}H_{17}O_3N_3$ requires C, 55·2; H, 7·15; N, 17·55%). The 2 : 4-*dinitrophenylhydrazone* formed orange needles, m. p. 136°, from aqueous ethanol (Found: N, 15·6. $C_{16}H_{18}O_6N_4$ requires N, 15·5%). The above cyclisation could also be effected by addition of the ester to cold aqueous alkali; the lactone separated and was crystallised as formed.

3-*Acetyl*-3 : 4 : 5 : 6-*tetrahydro*-4 : 6 : 6-*trimethyl*-1 : 2-*pyran*-2-*one* (III).—The pyrone (II) (20 g.) was hydrogenated in *iso*propanol (200 c.c.) in the presence of Raney nickel (8 g. of paste) at 70°. Hydrogen equivalent to 0·9 double bond was absorbed in 3 hr. Isolation of the product gave the *pyrone* (III) (17 g.), b. p. 80—83°/0·1 mm., n_D^{20} 1·4670, which subsequently solidified. Crystallisation from ether–light petroleum (b. p. 40—60°) gave plates, m. p. 56—57° (Found: C, 65·3; H, 8·85. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·75%), which produced a bright violet colour with ferric chloride.

4 : 6-*Dimethylhepta*-3 : 5-*dien*-2-*one* (IV).—A mixture of the pyrone (II) (30 g.) and sodium hydroxide solution (20%; 60 c.c.) was refluxed for 1 hr. Neutralisation with acetic acid, isolation with ether, and distillation gave mesityl oxide (3·2 g.) and a fraction, b. p. 83—86°/19 mm. (7·9 g.), redistillation of which gave two closely boiling fractions: (*a*) b. p. 78—80°/17 mm., n_D^{20} 1·4930, and (*b*) b. p. 80—83°/17 mm., n_D^{20} 1·5000, the latter being substantially pure *dienone* (IV) (Found: C, 77·8; H, 10·15. $C_9H_{14}O$ requires C, 78·2; H, 10·2%). A *semicarbazone* prepared from (*b*) formed plates, m. p. 153—154°, from aqueous methanol (Found: C, 61·85; H, 8·45; N, 21·6. $C_{10}H_{17}ON_3$ requires C, 61·5; H, 8·8; N, 21·5%). Light absorption: fraction (*a*): max., 2850 and 2250 Å.; ε, 12,500 and 10,700, respectively: fraction (*b*): max., 2850 Å; ε, 14,500.

3-*Acetyl*-5 : 6-*dihydro*-5 : 5-*dimethyl*-1 : 2-*pyran*-2-*one* (VI; R = H).—Diketen (44 g.) was added to a stirred mixture of freshly distilled β-hydroxy-αα-dimethylpropaldehyde (51 g.) and triethylamine (0·5 c.c.) at 55—65° during 45 min., which was then heated at 60° for a further 0·5 hr., and distilled. The product (62 g.) had b. p. 144—146°/12 mm., n_D^{20} 1·4594 (Found: C, 61·8; H, 7·45. Calc. for $C_9H_{14}O_4$: C, 58·5; H, 7·6. Calc. for $C_9H_{12}O_3$: C, 64·25; H, 7·2%). Repetition of the experiment, with triethylamine (3 c.c.) and toluene (150 c.c.), at the b. p., gave water (6 c.c.) and, on distillation, the *pyrone* (VI; R = H) (62·8 g., 75%), b. p. 144—148°/13 mm., n_D^{20} 1·4859 (Found: C, 64·1; H, 7·15. $C_9H_{12}O_3$ requires C, 64·25; H, 7·2%). Light absorption: max., 2300 Å; ε, 11,800. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol in orange needles, m. p. 183° (Found: C, 52·0; H, 4·35; N, 15·9. $C_{15}H_{16}O_6N_4$ requires C, 51·7; H, 4·65; N, 16·1%).

In this and in other experiments in which diketen was added to refluxing mixtures containing volatile amines, the diketen was introduced below the surface, otherwise some polymerisation took place on contact with the amine in the vapour.

3-*Acetyl*-5 : 6-*dihydro*-5 : 5-*dimethyl*-6-iso*propyl*-1 : 2-*pyran*-2-*one* (VI; R = Pr^i).—β-Hydroxy-αγ-dimethylvaleraldehyde (72 g.; prepared according to Späth, Lorenz, and Freund, *Ber.*, 1943, **76**, *B*, 1207; b. p. 92—96°/15 mm., n_D^{20} 1·4437) in boiling toluene (100 c.c.) containing triethylamine (3 c.c.) was treated with diketen (43·5 g.) during 45 min., and the product refluxed for a further 2 hr.: water (6·8 c.c.) was removed during the reaction. Distillation gave the *pyrone* (VI; R = Pr^i) (79·2 g., 77·5%), b. p. 119—122°/0·5 mm., n_D^{20} 1·4870 (Found: C, 68·25; H, 8·35. $C_{12}H_{18}O_3$ requires C, 68·55; H, 8·65%). The 2 : 4-*dinitrophenylhydrazone* crystallised from acetic acid as orange needles, m. p. 162—163° (Found: C, 55·3; H, 5·7; N, 14·0. $C_{18}H_{22}O_6N_4$ requires C, 55·35; H, 5·7; N, 14·35%).

3-*Acetylcoumarin* (VII; R = H).—Diketen (45 g.) was added during 1 hr. to an agitated refluxing mixture of salicylaldehyde (61 g.) and triethylamine (0·5 c.c.) in toluene (100 c.c.), and the mixture refluxed a further 0·5 hr., water (1 c.c.) being collected. Removal of solvents and washing of the residue with benzene–light petroleum (b. p. 40—60°) gave 3-acetylcoumarin (42 g., 45%), m. p. 122° (Knoevenagel, *loc. cit.*, gives m. p. 123°). Salicylaldehyde (19·4 g.) was recovered from the washings.

3-*Acetyl*-4-*methylcoumarin* (VII; R = Me).—Diketen (7 g., 98%) was condensed with *o*-hydroxyacetophenone (10 g.) in toluene (80 c.c.) and triethylamine (1 c.c.), and the product worked up as described in the previous experiment (crude yield: 4·3 g.). 3-*Acetyl*-4-*methylcoumarin* formed needles (from aqueous methanol), m. p. 102—103° (Found: C, 70·9; H, 5·0. $C_{12}H_{10}O_3$ requires C, 71·25; H, 5·0%). Light absorption: max., 2800 and 3200 Å; ε, 11,700 and 8700, respectively. The 2 : 4-*dinitrophenylhydrazone* crystallised from acetic acid in orange needles, m. p. 220—221° (Found: C, 56·3; H, 3·5; N, 14·8. $C_{18}H_{14}O_6N_4$ requires C, 56·55; H, 3·7; N, 14·65%).

3-*Oxobutyl Acetoacetate* (I; R = R′ = R″ = H).—4-Hydroxybutan-2-one (35·2 g.; prepared according to Hays, Hager, Engelmann, and Spurlin, *J. Amer. Chem. Soc.*, 1951, **73**, 5369) in chloroform (100 c.c.) containing trimethylamine (30% solution in methanol; 0·5 c.c.) was treated at 60° with diketen (34·6 g.). Distillation gave the *acetoacetate*, b. p. 117—120°/0·5 mm., n_D^{20} 1·4461, which was appreciably soluble in water (Found: C, 55·4; H, 7·35. $C_8H_{12}O_4$ requires C, 55·8; H, 7·05%).

1 : 2-*Dimethyl*-3-*oxobutyl Acetoacetate* (I; R = R″ = Me, R′ = H).—Diketen (44 g.) was added during 0·5 hr. to 4-hydroxy-3-methylpentane-2-one (58 g.) containing triethylamine (0·2 c.c.) at 65—75°, and the mixture then heated at 60° for a further 0·5 hr. Distillation gave the *acetoacetate* (86 g., 86%), b. p. 112—114°/0·5 mm., n_D^{20} 1·4460 (Found: C, 59·75; H, 7·9. $C_{10}H_{16}O_4$ requires C, 60·0; H, 8·05%).

3-*Acetyl*-2 : 5-*dihydro*-4 : 5-*dipropylfuran*-2-*one* (X; R = R′ = Pr^n).—(*a*) Diketen (31 g.) was added to a mixture of butyroin (48 g.), benzene (50 c.c.), and triethylamine (0·5 c.c.) at

60—70° during 0·5 hr. After a further hour at 60°, the product was distilled, giving fractions (i) 29·3 g., b. p. 132—157°/15 mm., and (ii) 16·8 g., b. p. 157—164°/15 mm. The second of these was redistilled, giving the pure *lactone*, b. p. 161—163°/15 mm., n_D^{20} 1·4847 (Found: C, 68·3; H, 8·7. $C_{12}H_{18}O_3$ requires C, 68·55; H, 8·65%). Light absorption: max. 2350 and 3110 Å; ε, 12,600 and 290, respectively. The 2 : 4-*dinitrophenylhydrazone* crystallised from *iso*propanol in red needles, m. p. 127° (Found: C, 55·25; H, 5·5; N, 14·3. $C_{18}H_{22}O_6N_4$ requires C, 55·4; H, 5·7; N, 14·35%).

(*b*) Repetition of the above under reflux, but with triethylamine (3 c.c.) and toluene (100 c.c.) in place of benzene, gave water (4 c.c.; after 2 hours' reaction). Distillation of the product gave the lactone (55·8 g., 80%), b. p. 158—165°/15 mm.

3-*Acetyl*-4 : 5-*diethyl*-2 : 5-*dihydrofuran*-2-*one* (X; R = R′ = Et).—The reaction of propionoin (56 g.) in toluene (100 c.c.) and triethylamine (3 c.c.) with diketen (45 g.) was carried out as in (*b*) above: 6·5 c.c. of water were collected. Distillation of the product gave the *lactone* (76·8 g., 84·5%), b. p. 140—142°/12 mm., n_D^{20} 1·4896 (Found: C, 65·7; H, 7·7. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·75%). Light absorption: max., 2300 and 3080 Å; ε, 25,100 and 710, respectively. The 2 : 4-*dinitrophenylhydrazone* formed red needles (from butanol), m. p. 140·5° (Found: C, 52·8; H, 4·8; N, 15·4. $C_{16}H_{18}O_6N_4$ requires C, 53·05; H, 5·0; N, 15·45%).

3-*Acetyl*-2 : 5-*dihydro*-4 : 5-*dimethylfuran*-2-*one* (X; R = R′ = Me).—Diketen (45 g.) was condensed with freshly distilled acetoin (36 g.) and triethylamine (1 c.c.) in toluene (80 c.c.) as described above: 6 c.c. of water were removed from the decanter head during the course of the reaction. Distillation gave the pale yellow *lactone* (52 g., 68·5%), b. p. 134—138°/12 mm., n_D^{20} 1·4915 (Found: C, 62·1; H, 6·85. $C_8H_{10}O_3$ requires C, 62·35; H, 6·55%). The 2 : 4-*dinitrophenylhydrazone* formed red prisms (from aqueous acetic acid), m. p. 177° (Found: C, 50·25; H, 3·9; N, 16·7. $C_{14}H_{14}O_6N_4$ requires C, 50·3; H, 4·2; N, 16·75%).

On prolonged storage, or, rapidly, when refluxed, in ethanol (20 c.c.) with a solution of sodium acetate (1 g.) in water (5 c.c.), the lactone (X; R = R′ = Me) (5 g.) gave a solid *dimer* (3·0 g.) which crystallised from aqueous methanol as needles, m. p. 240° (Found: C, 62·5; H, 7·0. $C_{16}H_{20}O_6$ requires C, 62·3; H, 6·55%). The dimer gave a 2 : 4-*dinitrophenylhydrazone* which crystallised as red needles, m. p. 270° (decomp.), from aqueous acetic acid (Found: C, 53·8; H, 5·2; N, 11·4. $C_{22}H_{24}O_9N_4$ requires C, 54·15; H, 4·95; N, 11·45%).

3-*Acetyl*-2 : 5-*dihydro*-4 : 5-*diundecylfuran*-2-*one* (X; R = R′ = $C_{11}H_{23}$).—Lauroin (110 g.) in toluene (200 c.c.) containing triethylamine (3 c.c.) was treated with diketen (27 g.) as previously described, water (6 c.c.) being eliminated. Removal of solvents gave an oil (129 g.).

3-*Acetyl*-2 : 4 : 5 : 6 : 7 : 8-*hexahydrobenzofuran*-2-*one* (XI).—Diketen (29 g.) was added during 0·75 hr. to a refluxing solution of 2-hydroxy*cyclo*hexanone (28·5 g.; prepared as described by Bloink and Pausacker, *J.*, 1950, 1330) in benzene (100 c.c.) and triethylamine (0·5 c.c.), and the mixture refluxed for a further 0·5 hr.; 3 c.c. of water were eliminated. Distillation gave the *lactone*, b. p. 124—126°/0·5 mm., n_D^{20} 1·5230 (Found: 66·3; H, 6·75. $C_{10}H_{12}O_3$ requires C, 66·65; H, 6·7%). Light absorption: max., 2370 Å; ε, 10,600. The 2 : 4-*dinitrophenylhydrazone* formed red needles, m. p. 196°, from ethyl acetate (Found: N, 15·3. $C_{16}H_{16}O_6N_4$ requires N, 15·55%).

3-*Acetyl*-2 : 5-*dihydro*-4 : 5-*diphenylfuran*-2-*one* (X; R = R′ = Ph).—Benzoin (53 g.) in toluene (80 c.c.) containing triethylamine (0·5 c.c.) was treated with diketen (22·5 g.) as previously described; 2·5 c.c. of water were eliminated. Removal of solvents and crystallisation of the residue (69 g.) from *iso*propanol gave the *lactone* as pale green needles, m. p. 109—110° (Found: C, 77·4; H, 4·9. $C_{18}H_{14}O_3$ requires C, 77·7; H, 5·05%). Light absorption: max., 3550 and 2900 Å; ε, 11,700 and 6700, respectively.

3-*Acetyl*-2 : 5-*dihydro*-4-*phenylfuran*-2-*one* (X; R = Ph, R′ = H).—Phenacyl alcohol was prepared by Evans's method (*Amer. Chem. J.*, 1906, **35**, 120), except that it was found that phenacyl acetate was not appreciably hydrolysed by boiling water; however, 1% hydrochloric acid was effective.

Diketen (8·6 g., 98%) was added during 1 hr. to an agitated solution of phenacyl alcohol (13·6 g.) in chloroform (20 c.c.) containing trimethylamine (0·2 c.c.; 25% in methanol) at 55—60°. After a further 20 min. at 55°, the solvent was evaporated and the residue (22 g.) crystallised from methanol, giving *phenacyl acetoacetate* as needles, m. p. 88° (Found: C, 65·35; H, 5·65. $C_{12}H_{10}O_3$ requires C, 65·45; H, 5·5%). The ester gave a weak yellow colour with ferric chloride.

The ester was cyclised by two methods: (*a*) The acetoacetate (5 g.) was refluxed in toluene (25 c.c.) and pyridine (1 c.c.) for 1 hr.; water was eliminated. Removal of solvents and crystallisation of the dark residue from aqueous methanol (charcoal) gave the *lactone* (3·0 g.), as yellow-

green needles, m. p. 107—108° (Found: C, 71·1; H, 4·85. $C_{12}H_{10}O_3$ requires C, 71·25; H, 5·0%). Light absorption: max., 2850 and 2250 Å; ε, 9550 and 5750, respectively.

(*b*) The ester (3 g.) was warmed for 1 hr. at 50° with methanol (10 c.c.) containing 10% aqueous sodium hydroxide (1 c.c.); isolation gave the lactone (1 g.).

Acetonyl Acetoacetate.—1-Hydroxypropan-2-one (23·5 g.), in benzene (100 c.c.) and triethylamine (0·2 c.c.), was treated with diketen (28 g., 98%) at 60—70°. Distillation gave the *acetoacetate* (23·0 g.), b. p. 98—100°/0·2 mm., n_D^{20} 1·4531 (Found: C, 53·5; H, 6·5. $C_7H_{10}O_4$ requires C, 53·15; H, 6·4%). Light absorption: max., 2300 Å; ε, 7000. When the ester was refluxed in toluene and pyridine water was eliminated and the product resinified. The *bis*-2 : 4-*dinitrophenylhydrazone* crystallised in orange granules, m. p. 208—209°, from aqueous acetic acid (Found: C, 43·7; H, 3·55; N, 22·0. $C_{19}H_{18}O_{10}N_8$ requires C, 44·0; H, 3·5; N, 21·6%).

Reaction of Acetoacetic Ester with Ketols.—(a) *Butyroin.* Butyroin (14·4 g.), methyl acetoacetate (11·6 g.), xylene (100 c.c.), pyridine (1 c.c.), and acetic acid (0·8 c.c.) were refluxed beneath a decanter head for 3 hr., during which 5 c.c. of aqueous alcohol were removed. Distillation gave the lactone (X; R = R′ = Pr^n) (14·2 g., 67·5%), b. p. 156—160°/12 mm., n_D^{20} 1·4835, which afforded a 2 : 4-dintrophenylhydrazone, m. p. and mixed m. p. 127°.

(b) *Benzoin.* Benzoin (53 g.), methyl acetoacetate (29 g.), piperidine (2 c.c.), and toluene (80 c.c.) were refluxed for 1·5 hr., aqueous methanol being eliminated as before. Removal of the solvent and recrystallisation of the residue from *iso*propanol gave the lactone (X; R = R′ = Ph) (39 g., 56%) as green needles, m. p. and mixed m. p. 109—110°.

(c) β-*Hydroxy*-α*γ*-*dimethylvaleraldehyde.*—The aldehyde (36 g.), methyl acetoacetate (35 g.), toluene (100 c.c.), piperidine (1 c.c.), and acetic acid (0·8 c.c.) were refluxed for 5 hr., 8·5 c.c. of aqueous methanol being removed from a decanter head. Distillation of the products gave the lactone (V; R = Pr^i) (29·8 g., 57%).

Hydration of 1-*Methylprop*-2-*ynyl Acetoacetate.*—Diketen (122 g., 97%) was added to an agitated mixture of but-3-yn-2-ol (98 g.) and triethylamine (0·5 c.c.) at 60—70° during 0·5 hr. Distillation gave the *acetoacetate* (177 g., 82%), b. p. 95—98°/12 mm., n_D^{20} 1·4441 (Found: C, 62·25; H, 6·95. $C_8H_{10}O_3$ requires C, 62·35; H, 6·55%). The ester (20 g.) was refluxed with a solution of mercuric chloride (1 g.) in aqueous ethanol (1 : 1; 50 c.c.) for 2 hr. Distillation gave α-*methylacetonyl acetoacetate* (8·0 g.), b. p. 124°/12 mm., n_D^{20} 1·4400 (Found: C, 56·15; H, 7·2. $C_8H_{12}O_4$ requires C, 55·8; H, 7·05%).

2 Hours' refluxing of the acetoacetate (8 g.) in toluene (20 c.c.) containing piperidine (0·5 c.c.) gave the lactone (X; R = R′ = Me) (6·1 g.), b. p. 135°/12 mm., shown to be identical with that previously obtained, by mixed-m. p. determinations on the 2 : 4-dinitrophenylhydrazones.

British Industrial Solvents,
Development Dept., Hedon, Hull.

[*Received, August 1st*, 1953.]

Derivatives of Acetoacetic Acid. Part II. The Rearrangement of 3-Acyl-2 : 5-dihydrofuran-2-one Derivatives to Furan-3-carboxylic Acids.*†

By R. N. Lacey.

[Reprint Order No. 4545.]

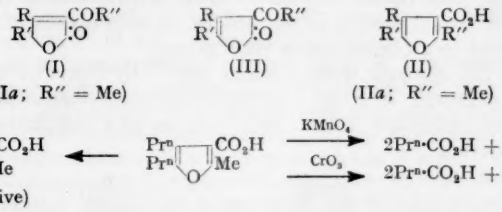
4 : 5-Dialkyl or -diaryl derivatives of 3-acetyl-2 : 5-dihydrofuran-2-one, when heated with a mixture of acetic and hydrochloric acids, gave 2-methyl-4 : 5-dialkyl(or diaryl)furan-3-carboxylic acids in high yield. Similarly, 3-benzoyl-2 : 5-dihydro-4 : 5-diphenylfuran-2-one, obtained by the piperidinium acetate-catalysed condensation of benzoin and methyl benzoylacetate, rearranged to 2 : 4 : 5-triphenylfuran-3-carboxylic acid.

Both 3-acetyl- and 3-benzoyl-2 : 5-dihydro-4 : 5-diphenylfuran-2-one autoxidised in air, giving, among other products, the 5-hydroxy-derivatives.

In Part I,* it was shown that aliphatic and aromatic acyloins condense with diketen and, though in somewhat poorer yields, with acetoacetic esters, to give unsaturated γ-lactones (I*a*). When the lactone (I*a*; R = R′ = Pr^n) was heated with a mixture of acetic acid and hydrochloric acid, a monobasic acid was obtained, which was isomeric with the

* Part I, preceding paper. † Patent pending: B.P. Appln. 14754/1951.

original lactone. Although it did not liberate hydrogen chloride from alcoholic hydroxylamine hydrochloride, when the acid was heated with a solution of 2 : 4-dinitrophenylhydrazine sulphate in aqueous ethanol, a solid bis-2 : 4-dinitrophenylhydrazone was obtained. Oxidation of the unknown acid with alkaline potassium permanganate gave *n*-butyric acid and oxalic acid (0·83 mol.); quantitative oxidation (Kuhn–Roth) showed a value of 2·42 terminal alkyl groups. The acid was unaffected both by boiling aqueous alkali and by hydrogen at atmospheric pressure and temperature in the presence of Raney nickel: the ultra-violet absorption spectrum had max. 2750 Å; ε, 7300. It was concluded that, under acid conditions, the lactone (I*a*; R = R′ = Pr^n) had rearranged to a β-furoic acid (II*a*; R = R′ = Pr^n); the reactions involved in the identification of the product are shown below. The acid gave a positive iodoform reaction, presumably by oxidative fission of the furan ring.



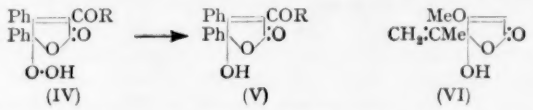
Similar rearrangements have been reported. Knorr and his co-workers (*Annalen*, 1898, **303**, 135; 1899, **306**, 355: *Ber.*, 1889, **22**, 165; 1894, **27**, 1158) and Kapf and Paal (*Ber.*, 1888, **21**, 3059; cf. Borsche and Fels, *Ber.*, 1906, **39**, 1813) have described the acid-catalysed rearrangement of βγ-unsaturated lactones of type (III) to substituted β-furoic acids. Bergel, Jacob, Todd, and Work (*J.*, 1939, 1375) have reported an analogous rearrangement in the conversion of a substituted α-stearoyl*iso*coumarone into an ethyl 2-heptadecylcoumarone-3-carboxylate in the presence of alcoholic hydrogen chloride.

Other lactones (I*a*), described in Part I, underwent similar rearrangement in acetic acid–hydrochloric acid. The lactone (I*a*; R = R′ = Et) gave a 73—80% yield of the β-furoic acid (II*a*; R = R′ = Et), m. p. 105—106°. Hydrochloric acid could be replaced by sulphuric acid, boron trifluoride etherate, or anhydrous aluminium trichloride. The rearrangement of the lactone (I*a*; R = R′ = Me) to the β-furoic acid (II*a*; R = R′ = Me), m. p. 130—131°, provided further evidence of the nature of the reaction, since the trimethyl-β-furoic acid had been synthesised by Reichstein, Zschokke, and Syz (*Helv. Chim. Acta*, 1932, **15**, 1112) by an authentic method. The identity of the lactone (I*a*; R = R′ = $C_{11}H_{23}$) obtained by the interaction of lauroin and diketen (see Part I) had not been established by analytical evidence, since the product was a high-boiling oil. Treatment of the crude lactone with hydrochloric acid in acetic acid gave a poor yield of a solid acid, m. p. 74°, which gave analytical data in satisfactory agreement with those expected for the β-furoic acid. The lactone (I*a*; R = R′ = Ph) very readily rearranged to the expected β-furoic acid; the use of sulphuric acid in acetic acid gave poorer yields, while the use of alcohols as solvents gave rise to mixtures, probably as a result of partial esterification of the acid formed.

Although the lactone (I*a*; R = R′ = Ph) could be stored indefinitely if air were excluded, after a few days in air it became yellow and gummy; also an acetic acid solution of the lactone, on agitation at 70°, rapidly absorbed oxygen. From the product obtained on keeping the lactone in contact with air for some weeks were isolated benzil, benzoic acid, acetic acid, and a solid acid, $C_{18}H_{14}O_4$. The last possessed a hydroxyl and a ·CO·CH_2· group, was ketonic, and gave no colour with ferric chloride. The ultra-violet absorption spectrum showed the keto-group to be αβ-unsaturated, although the intensity of the absorption band was low. It was concluded that the acid has the structure (V; R = Me), possessing the maleic acid half-aldehyde ring system.

As Shaw (*J. Amer. Chem. Soc.*, 1946, **68**, 2510) and Raphael (*J.*, 1947, 805) have shown for acetylacrylic acid and penicillic acid (VI), respectively, the cyclic formula adequately

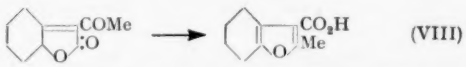
represents the acid character of such compounds. The acid (V; R = Me) was unaffected by boiling hydrochloric acid, but with alkali it formed an unidentified gum. Oxidation with alkaline potassium permanganate gave good yields of benzil and oxalic acid; the acid was unaffected by bromine in carbon tetrachloride. Clemmensen reduction gave



(IV) (V) (VI)

2-methyl-4 : 5-diphenylfuran-3-carboxylic acid (II*a*; R = R′ = Ph), the acid (V; R = Me) presumably being first reduced to the lactone (I*a*; R = R′ = Ph) which rearranged to the β-furoic acid. The acid (V; R = Me) probably arises, together with benzil, benzoic acid, and acetic acid, from the decomposition of the hydroperoxide (IV; R = Me), which, it is to be expected, would readily be formed by oxygen attack on the reactive tertiary carbon atom adjacent to a phenyl and a vinyl group.

The lactone (VII), derived from diketen and 2-hydroxy*cyclo*hexanone, readily rearranged to the expected 4 : 5 : 6 : 7-tetrahydro-2-methylbenzofuran-3-carboxylic acid (VIII) in acetic acid–hydrochloric acid, and, even on slow distillation at 2 mm., a partial conversion was achieved.

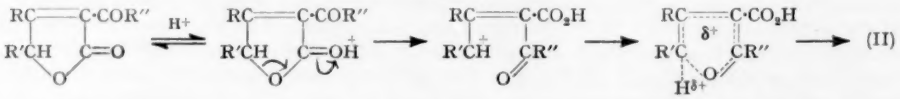


(VII) (VIII)

Despite the use of prolonged reaction times and anhydrous solutions, the rearrangement of the lactone (I*a*; R = Ph, R′ = H) could not be accomplished.

In Part I it has been shown that lactones (I*a*) can be prepared by the condensation of acyloins and acetoacetic ester. Similarly, the condensation of benzoin with methyl benzoylacetate in boiling xylene in the presence of piperidinium acetate gave the lactone (I; R = R′ = R″ = Ph). The results of analysis were unsatisfactory, and the ultraviolet spectrum failed to exhibit the expected strong absorption band at 3100 Å, characteristic of the PhC:C·COPh chromophore, being in better agreement with a formulation as the βγ-unsaturated lactone. Nevertheless, on treatment with acetic acid–hydrochloric acid at 100°, the lactone gave a good yield of 2 : 4 : 5-triphenylfuran-3-carboxylic acid (II; R = R′ = R″ = Ph), which was decarboxylated by the method of Reichstein *et al.* (*loc. cit.*) to the known 2 : 3 : 5-triphenylfuran (Japp and Klingemann, *J.*, 1890, 674). The lactone (I; R = R′ = R″ = Ph) absorbed oxygen from the air to give an acid, $C_{23}H_{16}O_4$ (V; R = Ph), possessing the cyclic maleic acid half-aldehyde structure.

It is thus apparent that lactones of type (I), or the corresponding βγ-unsaturated isomers, will rearrange to β-furoic acids under acid conditions if (*a*) R″ is methyl or phenyl, (*b*) R is alkyl, phenyl, carboxyl, ethoxycarbonyl, or hydrogen, and (*c*) R′ is alkyl or phenyl. When R′ was hydrogen, the lactone failed to rearrange. The evident activation of the reaction by a substituent in this last position suggested a Saytzeff type of elimination of the 'onium ion formed by the addition of a hydrogen ion to the ester grouping. The formation of a cyclic transition complex would then be followed by the elimination of hydrogen ion from C_5 (or C_3 in the case of a βγ-unsaturated lactone).



(II)

Clearly the nature of R can have only a minor influence on the reaction rate, since it can conjugate either with the starting material or with the product, but R′ can promote the reaction either by inductive effects (−*I*) * or by conjugation (or hyperconjugation) (−*E*) with the transition complex. The very large effects obtained in the reaction rate of

* Robinson sign convention.

triad anionotropy, obtained by substituents on the carbon atom originally attached to the anion, has been well illustrated (cf. Braude, *Quart. Reviews*, 1950, **4**, 404).

Experimental

M. p.s were determined in a Kofler block and are corrected. Light-absorption determinations were carried out in ethanol.

2-*Methyl*-4 : 5-*dipropylfuran*-3-*carboxylic Acid* (II*a*; R = R′ = Pr^n).—**3-Acetyl-2 : 5-dihydro-4 : 5-dipropylfuran-2-one** (I*a*; R = R′ = Pr^n) (5 g.) in acetic acid (30 c.c.) was added to concentrated hydrochloric acid (15 c.c.), and the mixture heated at 100° for 1 hr. Addition of water and storage, gave a white solid (4·8 g.; 96%), m. p. 61°, which crystallised from aqueous methanol as clusters of needles, m. p. 61°, of the **β-*furoic acid*** (II*a*; R = R′ = Pr^n) (Found: C, 68·25; H, 8·45%; acid equiv., 212. $C_{12}H_{18}O_3$ requires C, 68·55; H, 8·65%; equiv., 210·3). Treatment with aqueous-alcoholic 2 : 4-dinitrophenylhydrazine sulphate gave the ***bis*-2 : 4-*dinitrophenylhydrazone*** of 2 : 5-dioxo-4-propyloctane-3-carboxylic acid as dark red needles (from aqueous methanol), m. p. 113—114° (Found: C, 49·25; H, 5·2; N, 18·9. $C_{24}H_{28}O_{10}N_8$ requires C, 49·1; H, 4·8; N, 19·05%).

The acid (5 g.) in sodium carbonate solution (25 g. of 25% solution) was treated with potassium permanganate (14·4 g.) in water (200 c.c.) during 1 hr. with agitation and cooling. After a further 0·5 hr., the excess of potassium permanganate was destroyed with sodium hydrogen sulphite, the manganese dioxide filtered off, and the filtrate evaporated almost to dryness. Acidification gave *n*-butyric acid (*p*-bromophenacyl ester); evaporation to dryness and extraction of the residue with acetone gave oxalic acid dihydrate (2·5 g.), m. p. 100—101°. The Kuhn–Roth oxidation was carried out as described by Barthel and LaForge (*Ind. Eng. Chem. Anal.*, 1944, **16**, 434).

4 : 5-*Diethyl*-2-*methylfuran*-3-*carboxylic Acid* (II*a*; R = R′ = Et).—**3-Acetyl-4 : 5-diethyl-2 : 5-dihydrofuran-2-one** (I*a*; R = R′ = Et) (1 g.), acetic acid (10 c.c.), and concentrated hydrochloric acid (1 c.c.) were heated at 95—100° for 1 hr. Isolation as previously described gave the acid in 80% yield. Equivalent results were obtained by replacement of the acetic acid with dioxan whereas inferior results were obtained by replacement of the hydrochloric acid with aluminium trichloride (34%), boron trifluoride etherate (68%), or sulphuric acid (57%). The **β-*furoic acid*** formed prisms, m. p. 105—106°, from aqueous methanol (Found: C, 66·3; H, 7·45%; acid equiv., 179. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·75%; equiv., 182·2).

2 : 4 : 5-*Trimethylfuran*-3-*carboxylic Acid* (II*a*; R = R′ = Me).—**3-Acetyl-2 : 5-dihydro-4 : 5-dimethylfuran-2-one** (I*a*; R = R′ = Me) (3 g.), acetic acid (30 c.c.), and concentrated hydrochloric acid (15 c.c.) were heated at 100° for 0·5 hr. On pouring of the product into water, a crystalline precipitate (2·5 g., 83%), m. p. 129—130·5°, was obtained. The β-furoic acid formed prisms, m. p. 130—131°, from aqueous methanol [Reichstein *et al.*, *loc. cit.*, give m. p. 131—132° (corr.)].

2-*Methyl*-4 : 5-*diundecylfuran*-3-*carboxylic Acid* (II*a*; R = R′ = $C_{11}H_{23}$).—The crude product (50 g.) obtained from the reaction of lauroin and diketen (cf. Part I) was heated at 100° with acetic acid (100 c.c.) and concentrated hydrochloric acid (20 c.c.) with agitation (a homogeneous solution was not obtained) for 2 hr. On isolation, a semi-solid oil was obtained which was washed with dichloroethane and then crystallised from that solvent, giving the **β-*furoic acid*** as a white powder, m. p. 74° (Found: C, 77·0; H, 11·15%; acid equiv., 446. $C_{28}H_{50}O_3$ requires C, 77·35; H, 11·6%; equiv., 434·7).

2-*Methyl*-4 : 5-*diphenylfuran*-3-*carboxylic Acid* (II*a*; R = R′ = Ph).—**3-Acetyl-2 : 5-dihydro-4 : 5-diphenylfuran-2-one** (II*a*; R = R′ = Ph) (5 g.) in acetic acid (50 c.c.)–concentrated hydrochloric acid (5 c.c.) was heated at 100° for 1 hr., and the product was then cooled and filtered off; plates, m. p. 208° (3·2 g., 64%), were obtained: addition of water gave a crop (1·4 g.) of somewhat crude product. Crystallisation from ethyl acetate gave the **β-*furoic acid*** as plates, m. p. 212° (Found: C, 77·5; H, 5·0%; acid equiv., 273. $C_{18}H_{14}O_3$ requires C, 77·7; H, 5·05%; equiv., 275·3).

3-*Acetyl*-2 : 5-*dihydro*-5-*hydroxy*-4 : 5-*diphenylfuran*-2-*one* (V; R = Me).—After the lactone (II*a*; R = R′ = Ph) had been in contact with air for some weeks, the material was yellow and gummy, with a sharp smell of acetic acid. An ethereal solution of the product (20 g.) was extracted with aqueous sodium carbonate to give a non-acid oil (10·4 g.) and, by acidification of the sodium carbonate extract, an acid portion (8·4 g.). Vacuum distillation of the non-acid oil gave a fraction, b. p. 120—155°/1 mm. (3·1 g.), which, on crystallisation from light petroleum (b. p. 60—80°), gave benzil (1·0 g.) as pale yellow needles, m. p. and mixed m. p. 95—96°. Repeated crystallisation of the acid portion from benzene–light petroleum (b. p. 60—80°) gave

benzoic acid, m. p. 122°, and a second *acid* (V; R = Me), needles, m. p. 181° (Found: C, 73·6; H, 4·85. $C_{18}H_{14}O_4$ requires C, 73·45; H, 4·8%). Light absorption: max., 2600 Å; ε, 5730. A 2 : 4-*dinitrophenylhydrazone* crystallised from aqueous acetic acid as orange microcrystals, m. p. 204° (decomp.) (Found: N, 11·4. $C_{24}H_{18}O_7N_4$ requires N, 11·8%). Light absorption: max., 3720 Å; ε, 35,900 (cf. Braude and Jones, *J.*, 1945, 498). The acid gave no colour with ammonia solution, but afforded a *benzylthiuronium* salt as needles (from aqueous *iso*propanol), m. p. 103° (Found: N, 5·9. $C_{26}H_{24}O_4N_2S$ requires N, 6·1%). The acid (1 g.), acetyl chloride (1 c.c.), and pyridine (5 c.c.) were heated at 90° for 1 hr., giving the *acetate* (0·9 g.) which crystallised from ethyl acetate–light petroleum (b. p. 40—60°) as needles, m. p. 91—92° (Found: C, 71·55; H, 5·05. $C_{20}H_{16}O_5$ requires C, 71·4; H, 4·8%). Refluxing of the acid (0·25 g.) with benzaldehyde (0·1 g.) and aqueous sodium hydroxide (0·5 c.c. of 10%) in ethanol (5 c.c.) gave the *benzylidene* derivative (0·28 g. crude), needles, m. p. 185° (Found: C, 78·65; H, 4·6. $C_{25}H_{18}O_4$ requires C, 78·5; H, 4·75%). This derivative exhibited both acidic and ketonic properties. The acid (1·8 g.) in acetic acid (50 c.c.) was added to amalgamated zinc (from 4 g. of granulated zinc and 0·4 g. of mercuric chloride) and concentrated hydrochloric acid (10 c.c.), and the mixture refluxed for 5 hr., more (5 c.c.) concentrated hydrochloric acid being added after 3 and after 4 hr. Dilution and isolation with ether, and crystallisation of the product from benzene–light petroleum (b. p. 60—80°), gave needles (0·7 g.), m. p. 211° undepressed by a sample of 2-methyl-4 : 5-diphenylfuran-3-carboxylic acid (II*a*; R = R′ = Ph).

4 : 5 : 6 : 7-*Tetrahydro*-2-*methylbenzofuran*-3-*carboxylic Acid* (VIII).—3-Acetyl-2 : 4 : 5 : 6 : 7 : 8-hexahydrobenzofuran-2-one (VII) (3 g.) was heated at 100° for 1 hr. with acetic acid (20 c.c.)–concentrated hydrochloric acid (10 c.c.), and then poured into water. The precipitate (2·7 g., 90%) was crystallised from ethyl acetate–light petroleum (b. p. 60—80°) giving the β-*furoic acid* (VIII), m. p. 165—166° (Found: C, 67·0; H, 6·8%; acid equiv., 178. $C_{10}H_{12}O_3$ requires C, 66·65; H, 6·7%; equiv., 180·2). On slow distillation of (VII) at 2 mm. (bath temp. 160—170°), the later fractions, b. p. 140—145°/2 mm., partly crystallised, giving the same β-furoic acid.

3-*Benzoyl*-2 : 5(or 3)-*dihydro*-4 : 5-*diphenylfuran*-2-*one* (I; R = R′ = R″ = Ph).—A mixture of benzoin (21·2 g.), methyl benzoylacetate (27 g.), piperidine (1 c.c.), and acetic acid (0·8 c.c.) in xylene (100 c.c.) was refluxed for 5 hr. with the elimination of aqueous methanol (5·1 c.c.) collected in a Dean–Stark decanter head. When the solution cooled, unchanged benzoin (9·4 g.) was precipitated, but after partial evaporation, and crystallisation of the solid residue (10·8 g.) from ethyl acetate–light petroleum (b. p. 60—80°), the *lactone* was obtained as yellowish-green needles, m. p. 137—138°. Satisfactory microanalyses were not obtained (Found: C, 79·0, 80·1; H, 5·6, 5·0. $C_{23}H_{16}O_3$ requires C, 81·15; H, 4·75%). Light absorption: max. 2250 and 2700 Å; ε, 7800 and 8570, respectively.

3-*Benzoyl*-2 : 5-*dihydro*-5-*hydroxy*-4 : 5-*diphenylfuran*-2-*one* (V; R = Ph).—After several months' storage, the m. p. of the above lactone (I; R = R′ = R″ = Ph) had risen to 145—155°. The product (4·0 g.) in benzene–ethyl acetate (4 : 1; 100 c.c.) was adsorbed on activated alumina. Elution with the same solvent mixture gave a pale yellow product, m. p. 185—187° (3·09 g.), which, on crystallisation from ethyl acetate–light petroleum (b. p. 60—80°), gave the *acid* (V; R = Ph) as needles, m. p. 196°, soluble in sodium hydrogen carbonate solution (Found: C, 77·75; H, 4·45. $C_{23}H_{16}O_4$ requires C, 77·5; H, 4·55%). Light absorption: max. 2570 Å; ε, 20,000: infl. 2870 Å; ε, 14,000.

2 : 4 : 5-*Triphenylfuran*-3-*carboxylic Acid* (II; R = R′ = R″ = Ph).—The lactone (I; R = R′ = R″ = Ph) (2 g.) was heated at 100° for 1·5 hr. with acetic acid (10 c.c.)–concentrated hydrochloric acid (2 c.c.). Addition of water to the cooled solution and crystallisation of the precipitate (1·7 g.) from acetic acid gave the β-furoic acid (II; R = R′ = R″ = Ph), m. p. 257° (Found: C, 81·35; H, 4·95%; acid equiv., 331. Calc. for $C_{23}H_{16}O_3$: C, 81·15; H, 4·75%; Equiv., 340·4) (Adams and Melstrom, *J. Amer. Chem. Soc.*, 1946, **68**, 103, give m. p. 257—258°). The acid gave a strong blue fluorescence in water.

The β-furoic acid (0·5 g.) in diethylaniline (5 c.c.) was heated under reflux for 3 hr. with copper chromite catalyst (0·1 g.; Adkins, "Organic Syntheses," Wiley, Vol. II, p. 144): carbon dioxide was evolved. After cooling, the product was taken up in ether, the solution filtered, washed with dilute sulphuric acid followed by sodium hydrogen carbonate solution, and evaporated, and the residue (0·4 g.) crystallised from *iso*propanol, forming needles, m. p. 92—93° undepressed with a sample of 2 : 3 : 4-triphenylfuran prepared by Japp and Klingemann's method (*J.*, 1890, 674), who give m. p. 92—93°.

BRITISH INDUSTRIAL SOLVENTS, DEVELOPMENT DEPT.,
HEDON, HULL.

[*Received, August 1st*, 1953.]

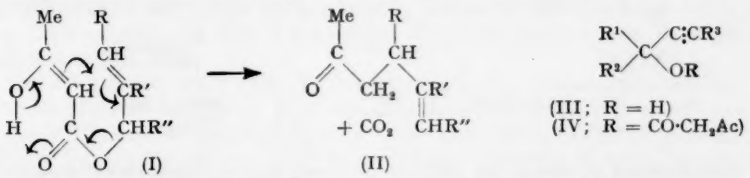
Derivatives of Acetoacetic Acid. Part III. The Pyrolysis of Acetoacetates of Ethynylcarbinols.†*

By R. N. Lacey.

[Reprint Order No. 4546.]

The acetoacetates of 3-methylbut-3-yn-2-ol, 3-methylpent-3-yn-2-ol, and 1-ethynyl*cyclo*hexanol were decarboxylated when heated in the presence of acids at 180—200°, giving 6-methylhepta-3 : 5-dien-2-one, 6-methylocta-3 : 5-dien-2-one, and 5-*cyclo*hexylidenepent-3-en-2-one, respectively. 1-Ethyl-1-methylhept-2-ynyl acetoacetate, an ester bearing a substituent in place of the ethynyl hydrogen atom, by contrast underwent the normal decarboxylation at 90—100° giving acetone and a vinylacetylene. 1 : 1-Dimethylprop-2-ynyl α-acetylbutyrate gave a low yield of dienone.

Until a few years ago, the only adequately described pyrolysis reaction of acetoacetic esters was the well-known formation of dehydroacetic acid and the parent alcohol (Arndt *et al.*, *Ber.*, 1924, **57**, 1489; 1936, **69**, 2377), a reaction which is observed when any acetoacetic ester is heated to about 150° or above, even when other reactions predominate. More recently, Kimel and Cope (*J. Amer. Chem. Soc.*, 1943, **65**, 1992), reinvestigating earlier observations by Caroll (*J.*, 1940, 704, 1266; 1941, 507), showed that allyl acetoacetate and its homologues (I) undergo decarboxylation when heated to about 200°, giving allylacetone and homologues (II). The nature of the products obtained from substituted allyl acetoacetates led the American authors to postulate a cyclic transition complex, the reaction being a further instance of the "allyl rearrangement" extensively studied by Cope and his collaborators. The pyrolysis of the acetoacetates of ethynylcarbinols (IV) forms the subject of the present paper, since it was considered possible that reactions analogous to those described for the esters of vinylcarbinols might take place, although it was realised that the resemblance might be only a formal one.



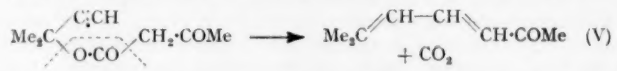
There are no previous references to the preparation of acetoacetates of ethynyl carbinols, but it was shown that the general use of diketen in the presence of a catalytic quantity of triethylamine made these esters very readily available. Prop-2-ynyl acetoacetate (IV; $R^1 = R^2 = R^3 = H$) was stable at 200° for short periods. In the presence of toluene-*p*-sulphonic acid at 180—190° there was only a very slow evolution of carbon dioxide and acetylene; and, even after being heated overnight, 40% of the ester was recovered and 45% converted into dehydroacetic acid. Similar results were obtained on heating 1-methylprop-2-ynyl acetoacetate (IV; $R^1 = Me$, $R^2 = R^3 = H$), although in the presence of toluene-*p*-sulphonic acid, a moderately fast evolution of gas was observed. However, distillation afforded only acetone, but-3-yn-2-ol, and dehydroacetic acid, with no significant quantity of material boiling in the range expected for a C_7 ketone.

1 : 1-Dimethylprop-2-ynyl acetoacetate (IV; $R^1 = R^2 = Me$, $R^3 = H$) was also stable at 200° for short periods, but, in the presence of a trace of toluene-*p*-sulphonic acid, there was a brisk evolution of gas, containing 87—93% of carbon dioxide plus some acetylene. Distillation gave dehydroacetic acid, 2-methylbut-3-yn-2-ol, and a 54% yield of 6-methylhepta-3 : 5-dien-2-one, which exhibited a strong absorption maximum in the ultra-violet at 2890 Å, characteristic of the C:C·C:C·C:O chromophore with three alkyl substituents, was hydrogenated to the known 6-methylheptan-2-one, and had physical properties similar to those reported by Kuhn and Hoffer (*Ber.*, 1932, **65**, *B*, 651).

* Part II, preceding paper. † Patent pending: B.P. Appln. 9355/1952.

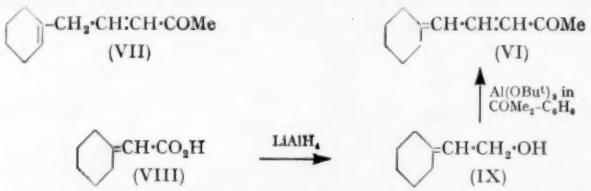
In the above reaction toluene-*p*-sulphonic acid can be replaced by sulphuric acid, phosphoric acid, or ferric chloride, and the pyrolysis can be carried out in the vapour phase at 320—340° by passing the ester through pumice granules impregnated with phosphoric acid.

1-Ethynyl-1-methylpropyl acetoacetate (IV; $R^1 = Me$, $R^2 = Et$, $R^3 = H$) was decarboxylated rapidly at 170—190° in the presence of toluene-*p*-sulphonic acid, giving a



50% yield of 6-methylocta-3 : 5-dien-2-one; this ketone exhibited a characteristic strong absorption band in the ultra-violet ($\lambda_{max.}$ 2880 Å), and when hydrogenated over Raney nickel previously washed with methanol containing 2% of acetic acid (cf. Weizmann, B.P. 574,446/1946) gave 6-methyloctan-2-one.

The acid-catalysed pyrolysis of 1-ethynyl*cyclo*hexyl acetoacetate at 180—200° afforded a 22·5% yield of 1-ethynyl*cyclo*hexanol and a 36% yield of a mixture of C_{11} ketones, boiling over a narrow range. Fractionation of this mixture gave material of widely varying refractive index, and examination of the ultra-violet absorption spectrum indicated that the product probably consisted of a mixture of the expected conjugated dienone (VI) and its isomer with an *endo*cyclic double bond (VII). Birch, Kon, and Norris (*J.*, 1923, 1361) showed that in the analogous case of *cyclo*hexenyl- and *cyclo*hexylideneacetone, the two isomers were very rapidly converted into an equilibrium mixture in the presence of alkali and were obtained pure only by regeneration from pure crystalline derivatives. Solid derivatives of (VI) were obtained, and hydrolysis of the semicarbazone by Kon's method (*J.*, 1930, 1616) gave pure 5-*cyclo*hexylidenepent-3-en-2-one, showing a single absorption maximum at 2900 Å.



An unambiguous synthesis of (VI) is outlined above. *cyclo*Hexylideneacetic acid (VIII) (cf. Schmid and Karrer, *Helv. Chim. Acta*, 1948, **31**, 1067) was reduced with lithium aluminium hydride to 2-*cyclo*hexylidene-ethanol (IX), previously prepared by the isomerisation of 1-vinyl*cyclo*hexanol (Dimroth, *Ber.*, 1938, **71**, *B*, 1333). (IX) was oxidised with aluminium *tert.*-butoxide in acetone–benzene and the product condensed with acetone to give (VI). Satisfactory analyses were not obtained for (VI) whether synthesised as above or as regenerated from the pure semicarbazone. Carbon and hydrogen figures were invariably low with all the compounds encountered of this type, probably owing to rapid auto-oxidation. Kuhn and Hoffer (*loc. cit.*) found that (V) rapidly resinified in air.

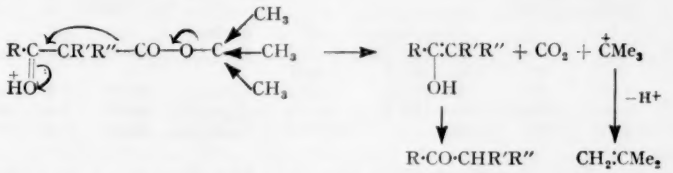
It was now of interest to examine whether the production of dienones by pyrolysis of *tert.*-ethynylcarbinols could be extended to esters in which the ethynyl hydrogen was replaced by alkyl. 1-Ethyl-1-methylhept-2-ynyl acetoacetate was prepared from diketen and the alcohol (III; $R^1 = Me$, $R^2 = Et$, $R^3 = Bu^n$) and, since on distillation at 1 mm. the product showed signs of decomposition, the crude ester was pyrolysed in the presence of toluene-*p*-sulphonic acid, without isolation. Gas evolution (95% carbon dioxide) was rapid at much lower temperatures (90—100°) than those employed in previous pyrolyses; distillation of the products afforded a 94% yield of acetone and a 64% yield of the substituted vinylacetylene, previously obtained by Thompson, Burr, and Shaw (*J. Amer. Chem. Soc.*, 1941, **63**, 186) by the vapour-phase dehydration of (III; $R^1 = Me$, $R^2 = Et$, $R^3 = Bu^n$).

Both the reaction conditions and the products are analogous to those met in the acid-catalysed pyrolysis of *tert.*-butyl esters of β-keto-acids (X) at 80—100° which gives *iso*butene, carbon dioxide, and a ketone (Yost and Hauser, *J. Amer. Chem. Soc.*, 1947, **69**, 2327; Renfrow and Walker, *ibid.*, 1948, **70**, 3957; Breslow, Baumgarten, and Hauser, *ibid.*, 1944, **66**, 1286; Fonken and Johnson, *ibid.*, 1952, **74**, 831; Libermann and Hengl, *Bull. Soc. chim.*, 1951, **18**, 974).

$$R{\cdot}CO{\cdot}CR'R''{\cdot}CO_2Bu^t \xrightarrow{H^+} R{\cdot}CO{\cdot}CHR'R'' + CO_2 + CH_2{:}CMe_2$$

(X) R = alkyl or aryl; R′ and R″ = H, alkyl, aryl, or CO_2R

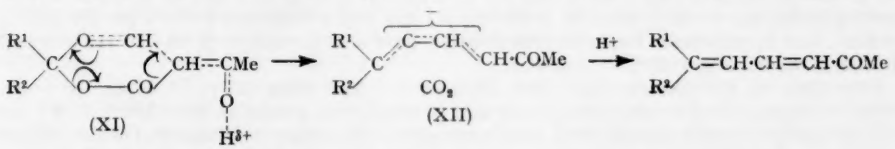
This reaction is confined to esters of *tert.*-alcohols and it must be supposed that the mechanism involves the addition of proton to the carbonyl oxygen, followed by electron migration towards this centre, the alkyl–oxygen ester linkage being loosened by the inductive effect of the three alkyl substituents.



That the acetoacetates of *tert.*-ethynylcarbinols possessing a free ethynyl hydrogen did not undergo this low-temperature decarboxylation must be attributed to the well-known electron-attracting influence of the ethynyl group, which would effectively prevent the postulated alkyl–oxygen fission. The retarding effect of the ethynyl group in three-carbon anionotropy as a result of its cationoid property has been well demonstrated by E. R. H. Jones, E. A. Braude, and their co-workers (cf. Braude, *Quart. Reviews*, 1950, **4**, 410). Substitution of the ethynyl hydrogen by alkyl would greatly reduce the electron-attracting influence of the group as a whole by virtue of the inductive effect of the substituent, thus enabling the normal low-temperature decarboxylation of an acetoacetate of a *tert.*-alcohol to take place.

When the α-ethyl derivative of 1 : 1-dimethylprop-2-ynyl acetoacetate was heated at 200—220° with toluene-*p*-sulphonic acid decarboxylation occurred only slowly and, even after 3 hr., only 0·74 mol. of carbon dioxide had been evolved. Distillation gave a product whose ultra-violet absorption spectrum indicated the expected dienone (estimated at about 25% yield), but it was contaminated with unchanged ester. Hydrogenation of the crude product gave 3-ethyl-6-methylheptan-2-one the structure of which was proved by independent synthesis.

It is suggested that the mechanism of the decarboxylation of *tert.*-alkynyl acetoacetates to give dienones involves first the acid-catalysed enolisation of the ester, followed by the ionisation of the enolic hydrogen and the formation of a partial bond between the ethynyl group and the α-carbon atom of the acetoacetic acid residue. The sharing of the electrons made available by the ionisation will reduce the electron-attracting properties of the ethynyl group, thus permitting the influences that caused the normal type of decarboxylation of *tert.*-alkyl acetoacetates to come into effect. Further, sharing of the electrons comprising the triple bond will permit the formation of a cyclic transition complex (XI),



thus further facilitating the formation of the anion (XII) which, on addition of proton, gives the dienone. The slow and incomplete reaction of the ester bearing an α-alkyl substituent would result from the lower enolisation tendency of such substituted esters.

Attention is drawn to the similarity between this reaction and the condensation of ethynylcarbinols with phenols (blocked in the *para*-position) to give chromens (Späth and co-workers, *Ber.*, 1939, **72**, 963, 2093; 1941, **74**, 193; Karrer, Legler, and Schwab, *Helv. Chim. Acta*, 1940, **23**, 1132). In both cases the reactions are acid catalysed, are confined to *tert.*-ethynyl derivatives, and involve the linkage of an ethynyl group to the carbon atom α- to an enolic (or phenolic) hydroxyl.

Experimental

M. p.s were determined on a Kofler block and are corrected. Light-absorption determinations were carried out in ethanol.

Preparation of Acetoacetates.—The acetoacetates were prepared by the dropwise addition of diketen (97—98%) to the agitated carbinol containing catalytic quantities of triethylamine. The results are tabulated below.

		Et_3N,	Yield,				Found, %		Reqd., %	
No.	Temp.	%	%	B. p./mm.	n_D^{20}	Formula	C	H	C	H
1	60—70°	0·13	83·5	97—100°/11	1·4551	$C_7H_8O_3$	60·15	5·85	60·0	5·75
2 [1]	60—70	0·17	82	95—98/12	1·4441	—	—	—	—	—
3 [2]	70	0·2	98·5	96—99/12	1·4462	$C_9H_{12}O_3$	64·35	7·3	64·25	7·2
4	70	0·2	83·5	110—116/14	1·4518	$C_{10}H_{14}O_3$	65·75	7·9	65·9	7·75
5	60—70	0·35	87	108/1	1·4796	$C_{13}H_{16}O_3$	69·5	7·95	69·2	7·75
6	70	0·15	—	—	—	—	—	—	—	—

1. III; $R^1 = R^2 = R^3 = H$. 2. III; $R^1 = Me$, $R^2 = R^3 = H$. 3. III; $R^1 = R^2 = Me$, $R^3 = H$. 4. III; $R^1 = Me$, $R^2 = Et$, $R^3 = H$. 5. III; $R^1R^2 = [CH_2]_5>$, $R^3 = H$. 6. III; $R^1 = Me$, $R^2 = Et$, $R^3 = Bu^n$.

[1] Previously described in Part I of this series.
[2] Subsequently solidified, plates, m. p. 49—49·5°, from light petroleum (b. p. 60—80°).

Pyrolysis of 1 : 1-*Dimethylprop*-2-*ynyl Acetoacetate*.—The ester (IV; $R^1 = R^2 = Me$, $R^3 = H$) (17 g.) and toluene-*p*-sulphonic acid (0·05 g.) were heated, by means of an oil bath at 170—180°, in a small flask fitted with a short air condenser. A rapid evolution of gas was observed, and, after 2·5 hr., 2·10 l. (at 18° and 758 mm.) of carbon dioxide (93% purity by analysis) were collected. Distillation of the liquid products, after the addition of anhydrous sodium acetate (0·1 g.), gave the following fractions: (*a*) (III; $R^1 = R^2 = Me$, $R^3 = H$), b. p. 100—110°/758 mm., 1·1 g., n_D^{20} 1·4210, (*b*) b. p. 85—90°/12 mm., 6·0 g., n_D^{20} 1·5184, and (*c*) b. p. 90—94°/12 mm., 0·7 g., n_D^{20} 1·5018. The yield of material, b. p. 85—94°/12 mm., was 54% (as $C_8H_{12}O$); redistillation gave 6-methylhepta-3 : 5-dien-2-one (V), b. p. 87—89°/12 mm., n_D^{20} 1·5265 (Kuhn and Hoffer, *loc. cit.*, give b. p. 86—90°/15 mm., n_D^{19} 1·5292) (Found: C, 76·9; H, 9·65. Calc. for $C_8H_{12}O$: C, 77·3; H, 9·75%). The oxime formed needles, m. p. 114—115°, from ethanol (Found: C, 68·75; H, 9·4. Calc. for $C_8H_{13}ON$: C, 69·0; H, 9·4%) [Kuhn and Hoffer, *loc. cit.*, give m. p. 108—109° (corr.)]. Light absorption of (V): max., 2890 Å; ε, 29,500.

The ketone (V) (6·2 g.) in methanol (20 c.c.) was agitated in hydrogen in the presence of Raney nickel (0·5 g. paste; washed with methanol containing 2% acetic acid) at 16°. 2·26 l. at 16°/760 mm. (theory, 2·37 l.) of gas were absorbed in 3 hr. Distillation gave 6-methylheptan-2-one, b. p. 164·5°, n_D^{20} 1·4162 (Hey and Morris, *J.*, 1948, 48, give b. p. 164—164·5°, n_D^{20} 1·4144). The m. p.s of the 2 : 4-dinitrophenylhydrazone, m. p. 74—75° (lit. m. p. 77°), and the semicarbazone, m. p. 152—153° (lit. m. p. 154—155°), were undepressed in admixtures with authentic specimens.

Replacement of toluene-*p*-sulphonic acid with (*a*) sulphuric acid (0·035 g.), gave a 46% yield (b. p. 87—95°/11 mm., n_D^{20} 1·4995) and 2·3 l. of gas (91% CO_2) in 3 hr., (*b*) phosphoric acid (0·05 g., 90%), gave a 55% yield (b. p. 83—85°/11 mm., n_D^{20} 1·5199) and 2·1 l. of gas (90% CO_2) in 3 hr., and (*c*) anhydrous ferric chloride (0·05 g.), gave a 12% yield (b. p. 86—90°/12 mm., n_D^{20} 1·5150) and 1·6 l. of gas (93% CO_2) in 4 hr.

Pyrolysis of 1 : 1-*Dimethylbut*-2-*ynyl Acetoacetate*.—The ester (IV; $R^1 = Me$, $R^2 = Et$, $R^3 = H$) (18·2 g.) and toluene-*p*-sulphonic acid (0·05 g.) were heated at 180—190°; 2·19 l. (at 18°/761 mm.) of carbon dioxide (96% pure) were collected in 70 min. Distillation of the product (12·75 g.), after addition of sodium acetate (0·1 g.), gave 2-methylpent-3-yn-2-ol (0·95 g.), b. p. 38—42°/14 mm., n_D^{20} 1·4400, and a main fraction (6·88 g., 50% yield) which, on redistillation, gave 6-*methylocta*-3 : 5-*dien*-2-*one*, b. p. 93—98°/14 mm., n_D^{20} 1·5212. Satisfactory analyses were not obtained (Found: C, 76·55; H, 9·95. $C_9H_{14}O$ requires C, 78·2; H, 10·2%). Light

absorption: max., 2880 Å; ε, 21,000. The 2:4-*dinitrophenylhydrazone* formed red needles, m. p. 183—185°, from acetic acid (Found: C, 56·35; H, 5·7; N, 17·4. $C_{15}H_{18}O_4N_4$ requires C, 56·6; H, 5·7; N, 17·6%).

6-Methylocta-3:5-dien-2-one (5·19 g.) and Raney nickel (0·5 g.; washed as previously described) in ethanol (20 c.c.) were agitated in hydrogen at 30—40° for 4·5 hr.; 1·735 l. (at 20°/750 mm.) had then been absorbed (theory 1·83 l.). Distillation of the product gave 6-*methyloctan*-2-*one* (3·67 g., 70·5%), b. p. 77—78°/16 mm., n_D^{20} 1·4265 (Found: C, 75·95; H, 12·55. $C_9H_{18}O$ requires C, 76·0; H, 12·75%). A 2:4-*dinitrophenylhydrazone* crystallised as yellow needles, m. p. 58°, from aqueous methanol (Found: C, 55·55; H, 6·8; N, 17·1. $C_{15}H_{22}O_4N_4$ requires C, 55·8; H, 6·85; N, 17·4%).

Pyrolysis of 1-*Ethynyl*cyclo*hexyl Acetoacetate*.—The acetoacetate (15 g.) and toluene-*p*-sulphonic acid (0·4 g.) were heated at 180—200° for 2 hr., 1·43 l. of gas (67% carbon dioxide) being evolved. After the addition of sodium acetate (0·2 g.), the product was distilled giving the following fractions: (*a*) 1-ethynyl*cyclo*hexanol, b. p. 77—80°/12 mm., n_D^{20} 1·4826 (2·01 g.); (*b*) b. p. 130—133°/12 mm., n_D^{20} 1·4169 (0·81 g.); (*c*) b. p. 133—135°/12 mm., n_D^{20} 1·4259 (1·97 g.); (*d*) b. p. 135—137°/12 mm., n_D^{20} 1·5381 (1·45 g.); and a residue of dehydroacetic acid. Light absorption: (*c*), max., 2330 and 2900 Å; ε, 15,400 and 12,000, respectively; (*d*), max., 2330 and 2900 Å; ε, 8400 and 13,000, respectively. The yield of material, b. p. 130—137°/12 mm., was 36%.

Fraction (*d*) gave a *semicarbazone* [plates, m. p. 204°, from aqueous ethanol (Found: C, 65·2; H, 8·2; N, 18·8. $C_{12}H_{19}ON_3$ requires C, 65·15; H, 8·65; N, 19·0%)] and a 2:4-*dinitrophenylhydrazone* [a dark red solid, m. p. 194° (decomp.), from aqueous acetic acid (Found: N, 16·5. $C_{17}H_{20}O_4N_4$ requires N, 16·3%)]. The semicarbazone (1·1 g.) was hydrolysed by aqueous sulphuric acid (20 c.c.; 0·5N) in boiling light petroleum (b. p. 60—80°) for 5 hr. with vigorous agitation, a clear solution being obtained. 5-cyclo*Hexylidenepent*-3-*en*-2-*one* (VI) (0·53 g.) had b. p. 94—95°/0·5 mm., n_D^{20} 1·5557. Unsatisfactory microanalyses were obtained (Found: C, 78·35, 78·7; H, 9·4, 9·45. $C_{11}H_{16}O$ requires C, 80·4; H, 9·8%). Light absorption: max. 2900 Å; ε, 27,800.

5-cyclo*Hexylidenepent*-3-*en*-2-*one*.—1-Hydroxy*cyclo*hexylacetic acid was prepared by the standard Reformatsky procedure ("Organic Reactions," Wiley, Vol. I, p. 17) followed by hydrolysis with aqueous alkali. It was converted into *cyclo*hexylideneacetic acid (VIII) as described by Schmid and Karrer (*loc. cit.*), but with a poorer yield (28%; lit. 42·2%).

*cyclo*Hexylideneacetic acid (23 g.) was added, in dry ether solution (350 c.c.), to an agitated, cooled solution of lithium aluminium hydride (9·3 g.) in dry ether (300 c.c.) during 0·5 hr. After a further 10 min., the excess of reagent was decomposed with ethyl acetate (50 g.), and the complex hydrolysed with saturated ammonium chloride solution (100 c.c.). After filtration, the product was isolated with ether, giving 2-*cyclo*hexylidene-ethanol (IX) (13·7 g., 66·7%), b. p. 101—106°/15 mm., n_D^{20} 1·4930 (Dimroth, *loc. cit.*, gives b. p. 95—96°/13·5 mm.). The 3:5-dinitrobenzoate had m. p. 90—91° (lit. m. p. 90—91°).

A mixture of 2-*cyclo*hexylidene-ethanol (10 g.), acetone (100 c.c.), aluminium *tert.*-butoxide (20 g.), and benzene (250 c.c.) was refluxed in an atmosphere of nitrogen for 48 hr. The product was cooled, shaken with water, and filtered. After being washed, the solvent layer was evaporated and the residue distilled, giving 5-*cyclo*hexylidenepent-3-en-2-one (5·26 g.), b. p. 102—106°/1 mm., n_D^{20} 1·5540, in addition to recovered *cyclo*hexylidene-ethanol (1·16 g.; b. p. 66—68°/1 mm.), and an intermediate fraction (1·19 g.; b. p. 68—102°/1 mm.). The semicarbazone had m. p. 204°, alone or in admixture with that derived from the ketone obtained in pyrolysis experiments.

Pyrolysis of 1:1-*Dimethylprop*-2-*ynyl* α-*Acetylbutyrate*.—1:1-Dimethylprop-2-ynyl acetoacetate (50·5 g.) was refluxed with ethyl iodide (51·5 g.) in a solution of potassium *tert.*-butoxide (from 11·7 g. of potassium in 180 c.c. of *tert.*-butanol). Titration of samples indicated that the reaction was substantially complete after 0·5 hr., and after 1 hr. the bulk of the solvent was evaporated, water added, and the product isolated with ether. Distillation gave 1:1-*dimethylprop*-2-*ynyl* α-*acetylbutyrate* (36·9 g., 62·5%), b. p. 105—110°/13 mm., n_D^{20} 1·4430 (Found: C, 67·65; H, 8·5. $C_{11}H_{16}O_3$ requires C, 67·3; H, 8·2%). Unexpectedly, the ester was insoluble in aqueous sodium hydroxide, gave no colour with ferric chloride, but gave a white precipitate with ammoniacal silver nitrate. The 2:4-*dinitrophenylhydrazone* formed pale orange microcrystals, m. p. 140°, from ethanol (Found: C, 54·5; H, 5·4; N, 14·9. $C_{17}H_{20}O_6N_4$ requires C, 54·25; H, 5·35; N, 14·9%).

The acetylbutyrate (11·8 g.) was heated with toluene-*p*-sulphonic acid (0·05 g.) at 200—220°: after 3 hr. 1·01 l. of gas (93% carbon dioxide) had been evolved. Distillation of the

residue (8·8 g.) gave fractions (*a*) b. p. 96—102°/10 mm., n_D^{20} 1·4715 (4·8 g.), (*b*) b. p. 102—105°/10 mm., n_D^{20} 1·4600 (2·5 g.), and high-boiling material. Fraction (*b*) consisted substantially of unchanged ester, while (*a*) comprised ester with 40—50% of a dienone, as indicated by the light absorption: max., 2910 Å; ε, 10,000.

The mixed products, b. p. 96—105°/10 mm., were hydrogenated in methanol in the presence of "acid-washed" Raney nickel until absorption ceased. Distillation gave a fraction (31% of total), b. p. 72—78°/10 mm., n_D^{20} 1·4255, which gave a *semicarbazone* (from aqueous methanol), m. p. 87° (Found: C, 62·1; H, 10·55; N, 19·7. $C_{11}H_{23}ON_3$ requires C, 61·95; H, 10·85; N, 19·7%). This did not depress the m. p. of the derivative of authentic 3-ethyl-6-methylheptan-2-one.

3-Ethyl-6-methylheptan-2-one.—Ethyl α-acetylbutyrate (79 g.) was refluxed with *iso*pentyl bromide (83 g.) in the presence of potassium *tert.*-butoxide (from 19·5 g. of potassium in 250 c.c. of *tert.*-butanol) for 3 hr. Isolation gave *ethyl 3-acetyl-6-methylheptane-3-carboxylate* (62·8 g., 55%), b. p. 123—128°/12 mm., n_D^{20} 1·4375 (Found: C, 68·35; H, 10·75. $C_{13}H_{24}O_3$ requires C, 68·4; H, 10·6%).

The ester was hydrolysed by the method employed by Renfrow (*J. Amer. Chem. Soc.*, 1944, **66**, 146) for the "ketonic" hydrolysis of disubstituted acetoacetic esters, giving *3-ethyl-6-methylheptan-2-one* (54% yield), b. p. 70—72°/11 mm., n_D^{20} 1·4230 (Found: C, 76·9; H, 13·0. $C_{10}H_{20}O$ requires C, 76·85; H, 12·9%). The semicarbazone (see above) had m. p. 87°.

BRITISH INDUSTRIAL SOLVENTS, DEVELOPMENT DEPT.,
HEDON, HULL.

[*Received, August 1st*, 1953.]

Derivatives of Acetoacetic Acid. Part IV. A New Route to α-Acetyltetronic Acids.†*

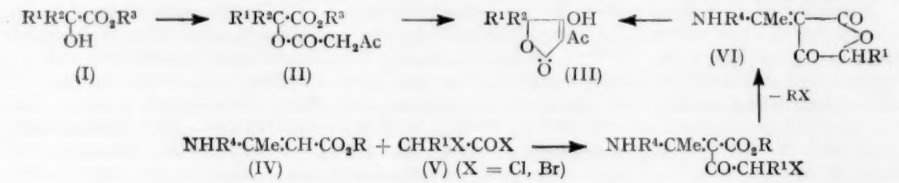
By R. N. LACEY.

[Reprint Order No. 4547.]

Substituted α-acetyltetronic acids were readily prepared by the Dieckmann-type cyclisation of the acetoacetates of α-hydroxy-esters: almost quantitative yields were obtained by the cyclisation of the acetoacetates of *tert.*-α-hydroxy-esters with sodium alkoxide in an alcoholic medium. Bromination of α-acetyltetronic acids in aqueous acetic acid gave α-bromotetronic acids, which could be catalytically reduced to the corresponding tetronic acids. α-Acetyltetronic acids reacted with ammonia and primary amines to give the α-aminoethylidene derivatives.

As part of the study of acetoacetates of alcohols possessing a second reactive grouping, the self-condensation was attempted of the acetoacetates of α-hydroxy-esters by a Dieckmann type of cyclisation of the alkoxycarbonyl group on to the reactive methylene group of the acetoacetic acid residue, which might be expected to provide a new route to α-acetyltetronic acids (III).

The acetoacetate of ethyl lactate was cyclised by use of sodium in toluene, facilities for the removal of lower-boiling products being provided in order to avoid alcoholysis of the



acetoacetate with the alcohol eliminated in the course of the reaction. The α-acetyl-γ-methyltetronic acid (III; R^1 = Me, R^2 = H), m. p. 54—55°, was obtained in 50% yield.

* Part III, preceding paper.

† Patents pending: B.P. Appln. 110/1951, 4251/1952, and 18779/1952.

Other experimental conditions afforded lower yields: sodium in methanol–benzene gave a 20% yield, sodium in *tert.*-butanol a 30% yield, and potassium in *tert.*-butanol a 46% yield.

The only previously described method for the synthesis of α-acetyltetronic acids, that due to Benary (*Ber.*, 1909, **42**, 3912; cf. also Baker, Grice, and Jensen, *J.*, 1943, 241; Lecocq, *Compt. rend.*, 1946, **222**, 183), involves the reaction of a β-aminocrotonate (IV) with an α-halogeno-acid halide (V) in the presence of pyridine, followed by cyclisation to (VI) and, finally, alkaline hydrolysis to (III). Baker *et al.* (*loc. cit.*) record an overall yield of 34% of α-acetyltetronic acid by this route.

Methyl mandelate reacted smoothly with diketen to give a quantitative yield of the acetoacetate (II; R^1 = Ph, R^2 = H, R^3 = Me), m. p. 56°; cyclisation by means of sodium in toluene gave α-acetyl-γ-phenyltetronic acid, m. p. 104—105°, in 55% yield.

γγ-Disubstituted α-acetyltetronic acids were also readily made by this new method. The acetoacetate of methyl α-hydroxy*iso*butyrate with sodium in toluene gave a 67% yield of α-acetyl-γγ-dimethyltetronic acid; use of sodium ethoxide in toluene–ethanol increased the yield to 92%. Methyl α-hydroxy*iso*butyrate was therefore allowed to react with methyl acetoacetate in the presence of alcoholic sodium ethoxide, it being hoped that alcoholysis would give rise to the acetoacetate (II), which would then be rapidly converted into the α-acetyltetronic acid. However, only unchanged materials were isolated. On the other hand, in a similar experiment with ethyl lactate and methyl acetoacetate in alcoholic sodium ethoxide, a small yield (10%) of α-acetyl-γ-methyltetronic acid was obtained.

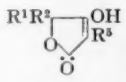
$$\underset{\text{(I)}}{R^1R^2C(OH)CO_2R^3} + CH_2Ac\cdot CO_2R \rightleftharpoons \underset{\text{(II)}}{R^1R^2C(O\cdot CO\cdot CH_2Ac)CO_2R^3} + ROH$$

An explanation of these results may be found by consideration of the alcoholysis equilibrium shown above. Acetoacetic esters undergo alcoholysis, even in the absence of catalyst, with great ease (Bader, Cummings, and Vogel, *J. Amer. Chem. Soc.*, 1951, **73**, 4195; Bader and Vogel, *ibid.*, 1952, **74**, 3992). Further, esters of *tert.*-alcohols undergo alkaline hydrolysis at a far lower rate than do those of *sec.*-alcohols (the rates for the hydrolysis of *iso*propyl acetate and *tert.*-butyl acetate, as quoted by Hammett, "Physical Organic Chemistry," McGraw-Hill, 1940, p. 211, are in the ratio 17·3 : 1), and, since the mechanisms are known to be similar, it is to be expected that similar considerations must hold for alcoholysis reactions. Thus, in an alcoholic medium, rapid alcoholysis of (II) to (I) will ensue if (II) is an ester of a *sec.*-alcohol, and, the cyclisation to α-acetyltetronic acid, being a slower reaction, only a poor yield of (III) will be obtained; although if the reaction medium is itself a *tert.*-alcohol the alcoholysis will be slower and a higher yield of acetyltetronic acid afforded. However, starting with an acetoacetate of a *tert.*-α-hydroxy-ester, the alcoholysis reaction will be much slower, permitting a high yield of α-acetyltetronic acid, while the slow alcoholysis reaction will effectively prevent the formation of α-acetyltetronic acid from a *tert.*-α-hydroxy-ester but permit a small yield from a *sec.*-α-hydroxy-ester.

In other experiments, high yields of α-acetyltetronic acids were obtained by cyclisation of acetoacetates of *tert.*-α-hydroxy-esters in alcoholic media; it is probable that purely mechanical factors (insoluble sodium salts) caused the lower yields obtained by use of sodium in benzene or toluene. Cyclisation of the acetoacetate of methyl benzilate by sodium ethoxide in ethanol–benzene gave α-acetyl-γγ-diphenyltetronic acid (III; R^1 = R^2 = Ph) in 88·5% yield; the acetoacetate of methyl 1-hydroxy*cyclo*hexanecarboxylate similarly gave a 95% yield of the α-acetyltetronic acid (III; R^1R^2 = $[CH_2]_5$>) and the use of sodium *n*-butoxide in *n*-butanol gave an almost quantitative yield. The generality of the new route was illustrated by the cyclisation of the acetoacetate (II; R^1 = R^3 = Me, R^2 = CH_2Ph) into α-acetyl-γ-benzyl-γ-methyltetronic acid again in good yield.

Attempts to extend this reaction to β-hydroxy-esters were unsuccessful. While ethyl β-hydroxybutyrate readily afforded an acetoacetate, attempted cyclisation of that ester with sodium in toluene gave only crotonic and dehydroacetic acids as recognisable products. Methyl salicylate, which might be expected to afford 3-acetyl-4-hydroxycoumarin, failed

to react with diketen in the presence of either acidic or basic catalysts, presumably as a result of steric hindrance.



(VII; $R^1 = Me$, $R^2 = H$, $R^5 = CO{\cdot}[CH_2]_2{\cdot}CH_2{\cdot}OH$)
(VIII; $R^1 = Me$, $R^2 = H$, $R^5 = CO{\cdot}CHBr{\cdot}CH_2{\cdot}CH_2{\cdot}OH$)
(IX; $R^1 = Me$, $R^2 = H$, $R^5 = CO{\cdot}CH_2Br$)
(X; $R^1 = Me$, $R^2 = H$, $R^5 = Br$)
(XI; $R^1 = R^2 = Me$, $R^5 = Br$)
(XII; $R^1 = R^2 = Me$, $R^5 = H$)
(XIII; $R^1R^2 = [CH_2]_5>$, $R^5 = Br$)
(XIV; $R^1R^2 = [CH_2]_5>$, $R^5 = H$)

The behaviour of α-acyltetronic acids on bromination has previously been studied by Clutterbuck, Raistrick, and Reuter (*Biochem. J.*, 1935, **29**, 300); it was shown that (+)-carolic acid (VII; shown as its hydrated form), on treatment with one mol. of bromine in acetic acid, gave (+)-monobromocarolic acid (VIII), and, that further bromination in aqueous acetic acid resulted in the removal of the side-chain and the formation of (+)-α-bromo-γ-methyltetronic acid (X).

α-Acetyl-γ-methyltetronic acid behaved analogously, giving α-bromoacetyl-γ-methyltetronic acid (XI) and α-bromo-γ-methyltetronic acid, the latter the (±)-form of that obtained from carolic acid by Clutterbuck *et al.* (*loc. cit.*). Similarly, α-acetyl-γγ-dimethyltetronic acid and α-acetyl-γ-*spirocyclo*hexanetetronic acid with two mols. of bromine in aqueous acetic acid gave α-bromo-γγ-dimethyltetronic acid (XI) and α-bromo-γ-*spirocyclo*hexanetetronic acid (XIII), respectively. Catalytic reduction of the α-bromotetronic acids (Clutterbuck *et al.*, *loc. cit.*; Reuter and Welch, *J. Proc. Roy. Soc. N.S. Wales*, 1939, **72**, 120) gave the known γγ-dimethyltetronic acid (XII) and γ-*spirocyclo*hexanetetronic acid (XIV).

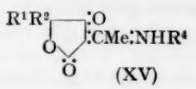
The α-acetyltetronic acids readily formed ketonic derivatives which, as has been shown for α-acetyltetronic acid itself by Benary (*Ber.*, 1910, **43**, 1065), involve the side-chain carbonyl group. Thus, the phenylhydrazones and semicarbazones are soluble in sodium hydrogen carbonate solution and colour ferric chloride solutions red, indicating a formula (XVI), where $R^4 = NHPh$ or $NH{\cdot}CO{\cdot}NH_2$. Benary had found that acetyl chloride and α-acetyltetronic acid phenylhydrazone gave a pyrazolone. However, we found that this reagent with the phenylhydrazones of α-acetyl-γ-methyltetronic acid and of the γ-phenyl analogue gave the *O*-acetyl derivatives. In contrast, the α-acetyltetronic acids themselves are unaffected by acetyl chloride (cf. Clutterbuck *et al.*, *loc. cit.*), recalling the non-reactivity of the hydroxy-group in analogous derivatives of 3-acetyl-4-hydroxycoumarin (Heilbron and Hill, *J.*, 1927, 1705). This behaviour is possibly attributable to hydrogen-bonding of the hydroxyl group with the acetyl group.

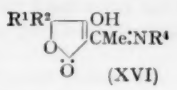
Wide differences were exhibited by α-acetyltetronic acids on hydrolysis. While a small yield of γ-methyltetronic acid was obtained by alkaline hydrolysis of α-acetyl-γ-methyltetronic acid, similar treatment of the γ-phenyl and γγ-dimethyl analogues resulted in extensive break-down. On the other hand, the γ-*spirocyclo*hexane- and γ-benzyl-γ-methyl derivatives were substantially unaffected by boiling 10% sodium hydroxide, and the former resisted even boiling concentrated hydrochloric acid and 80% sulphuric acid at 100°. Only with α-acetyl-γγ-diphenyltetronic acid were good results obtained, a 61% yield of γγ-diphenyltetronic acid being obtained by hydrolysis with cold aqueous alkali.

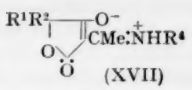
Benary (*Ber.*, 1909, **42**, 3918) found that heating of α-acetyltetronic acid with aniline gave (VI; $R^1 = H$, $R^4 = Ph$) that had previously been obtained as an intermediate in his synthesis. This is a general reaction of α-acetyltetronic acids which readily afford "amides" with ammonia and primary amines: secondary amines, however, gave salts. Benary has suggested that since the "amides" are neutral compounds affording no colour with ferric chloride, but are soluble in sodium hydroxide solution (this we have confirmed only in certain cases), they possess the structure (XV), but readily rearrange to the ketimine (XVI) with alkali. Light-absorption determination (see Table) give clear evidence in favour of structure (XV), since the "amides" derived from ammonia and aliphatic amines exhibit strong absorption bands at 2250—2310 Å and 2830—2940 Å. The latter band is incompatible with the ketimine structure (XVI), but is to be expected for the system N·C:C·C:O possessed by (XV), the shift to higher wave-lengths arising from the

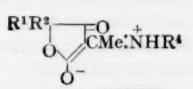
auxochromic effect of the amino-substituent (Bowden, Braude, Jones, and Weedon, *J.*, 1946, 45; Bowden, Braude, and Jones, *ibid.*, p. 948). The bands exhibited by the α-acetyltetronic acid amides at 2250—2310 Å, which are considerably more intense than the absorption exhibited in this region by the aminocrotonic esters, may be attributable to interaction of the carbonyl and carboxyl groups in the dipolar resonance forms (XVII and XVIII).

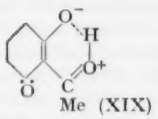
α-Acetyltetronic acids exhibit two absorption bands at 2300—2360 and at 2600—2680 Å (cf. Herbert and Hirst, *Biochem. J.*, 1935, **29**, 1881). Similar behaviour has been

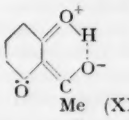

(XV)


(XVI)


(XVII)


(XVIII)


(XIX)


(XX)

noted in the case of enolised β-triketones (Birch and Todd, *J.*, 1952, 3102), and Smith (*J.*, 1953, 803) has ascribed the bands exhibited by 2-acetyl*cyclo*hexane-1 : 3-dione at 2350 and 2750 Å (in methanol), respectively, to the αβ-unsaturated carbonyl group and the conjugated diene chromophore in a ring formed by an intramolecular hydrogen bond, as in (XIX) and (XX). Comparison (see Table) of the spectra of α-acetyltetronic acids

Light-absorption data (in ethanolic solution).

α-Acetyltetronic acids.

	$\lambda_{max.}$, Å	$\varepsilon_{max.}$	$\lambda_{max.}$, Å	$\varepsilon_{max.}$
(III; $R^1 = R^2 = H$) [1]	2300	15,000	2650	15,000
(III; R^1 = Me, R^2 = H)	2300	9,100	2600	12,000
(III; $R^1 = R^2$ = Me)	2300	9,500	2640	13,800
(III; R^1 = Ph, R^2 = H)	2360	12,000	2670	15,150
(III; $R^1 = R^2$ = Ph)	2300	10,050	2680	17,000
(III; $R^1R^2 = [CH_2]_5$>)	2300	10,050	2660	14,500
(III; $R^1 = CH_2Ph$, R^2 = H)	2300	9,800	2650	16,000
γγ-Dimethyltetronic acid (XII) [2]	2230	13,500	—	—
HO·CMe:CHAc [3]	2690	12,000	—	—

[1] Herbert and Hirst, *loc. cit.*, determined in water. [2] Jones and Whiting, *J.*, 1949, 1419. [3] Grossmann, *Z. physikal. Chem.*, 1924, **109**, 305, determined in hexane.

Enamines.

	$\lambda_{max.}$, Å	$\varepsilon_{max.}$	$\lambda_{max.}$, Å	$\varepsilon_{max.}$
(XVI; $R^1 = R^2$ = Me, R^3 = H)	2250	8,700	2830	20,000
(XVI; $R^1R^3 = [CH_2]_5$>, R^3 = Me)	2290	11,000	2910	27,700
(XVI; $R^1 = R^3$ = Ph, R^3 = Me)	2310	11,500	2940	25,000
(XVI; R^1 = Ph, R^2 = H, R^3 = Ph)	2300	11,600	3050	23,000
Et_2N·CMe:CH·CO_2Et [1]	2850	30,500	2880	30,500
NHPh·CMe:CH·CO_2Et [2]	2940	11,500	—	—

[1] Bowden, Braude, Jones, and Weedon, *loc. cit.* [2] Jones and Whiting, *J.*, 1949, 1423.

with those of γγ-dimethyltetronic acid and acetylacetone shows that the bands at 2300—2360 Å are to be associated with interaction between the enol double bond and the carboxyl group, and that the bands at 2600—2680 Å can be attributed to the HO·C:C·CO·CH_3 chromophore. Exaltation of the absorption band observed in the latter case must be due partly to the auxochromic effect of the HO substituent but chiefly to the increased resonance arising from intramolecular hydrogen bonding.

Calam, Todd, and Waring (*Biochem. J.*, 1949, **45**, 520) found that anhydrotetronic acid possessed appreciable activity in causing the hatching of the potato-root eelworm (*Heterodera rostochiensis*), although it was much less active than the naturally secreted agent. The following α-acetyltetronic acids were tested by Dr. D. W. Fenwick of the Nematology Department, Rothamstead Experimental Station: III; R^1 = Me, R^2 = H; R^1 = Ph,

$R^2 = H$; $R^1 = R^2 = Me$; $R^1 = R^2 = Ph$. Dr. Fenwick concluded that none of the four compounds was capable of stimulating larval emergence in *Heterodera rostochiensis* under *in vitro* conditions.

Experimental

M. p.s were determined on a Kofler block and are corrected.

Acetoacetate of Ethyl Lactate (II; $R^1 = Me$, $R^2 = H$, $R^3 = Et$).—To an agitated mixture of ethyl lactate (59 g.) and triethylamine (0·5 c.c.) at 65—75° diketen (42 g.) was added during 1 hr., and the product was then heated for a further ½ hr. Distillation gave the *ester* (89·3 g., 89%), b. p. 132—136°/14 mm., n_D^{20} 1·4350 (Found: C, 53·5; H, 7·15. $C_9H_{14}O_5$ requires C, 53·45; H, 7·0%).

α-Acetyl-γ-methyltetronic Acid (III; $R^1 = Me$, $R^2 = H$).—Sodium (11·5 g.) was rapidly added to an agitated mixture of the above ester (101 g.) and toluene (150 c.c.), which was then gently heated under a short fractionating column with a total reflux still-head; a vigorous reaction ensued with deposition of solid sodium salts. Gentle heating was continued for 1 hr. during which material, b. p. 70—90° (20 c.c.), was removed from the still-head. Next morning, aqueous hydrochloric acid (50 c.c. of acid and 50 c.c. of water) was added with cooling. Thorough extraction with ether, followed by distillation, afforded the tetronic acid (39·5 g., 50%), b. p. 120—126°/15 mm., m. p. 54—55° [from ether–light petroleum (b. p. 60—80°)] (Lecocq, *loc. cit.*, gives m. p. 55°) (Found: C, 53·9; H, 5·1. Calc. for $C_7H_8O_4$: C, 53·85; H, 5·15%). Cyclisation of the acetoacetate (50·5 g.) by refluxing it for 2 hr. with sodium *tert.*-butoxide (from 5·75 g. of sodium and 150 c.c. of *tert.*-butanol) gave a 30%, and the use of potassium *tert.*-butoxide (from 9·8 g. of potassium and 150 c.c. of *tert.*-butanol) a 46% yield.

The reaction of α-acetyl-γ-methyltetronic acid (1·5 g.) with phenylhydrazine (1 g.) in boiling benzene (10 c.c.) for 10 min., followed by addition of light petroleum and cooling, gave the *phenylhydrazone* (2·0 g.), m. p. 165° [from ethyl acetate–light petroleum (b. p. 60—80°)] (Found: C, 63·35; H, 5·6; N, 11·3. $C_{13}H_{14}O_3N_2$ requires C, 63·4; H, 5·75; N, 11·4%). When the phenylhydrazone (4·5 g.) was refluxed in chloroform (30 c.c.) with acetyl chloride (3 g.) for 3 hr., there was obtained the *acetyl* derivative (3·8 g.), m. p. 175° [from ethyl acetate–light petroleum (b. p. 40—60°)] (Found: C, 62·0; H, 5·45; N, 9·95. $C_{15}H_{16}O_4N_2$ requires C, 62·5; H, 5·6; N, 9·7%).

α-Acetyl-γ-methyltetronic acid (5 g.), methanol (10 c.c.), and ammonia solution (*d* 0·88; 5 c.c.) were refluxed for 1 hr., and then concentrated. The amide (XV; $R^1 = Me$, $R^2 = R^4 = H$) (1·9 g.) crystallised from *n*-butanol as needles, m. p. 159—160° (Lecocq, *loc. cit.*, gives m. p. 161°) (Found: C, 54·4; H, 5·75. Calc. for $C_7H_9O_3N$: C, 54·2; H, 5·85%).

Acetoacetate of Methyl Mandelate (II; $R^1 = Ph$, $R^2 = H$, $R^3 = Me$).—Methyl mandelate was prepared from mandelic acid and methanol by Clinton and Laskowski's method (*J. Amer. Chem. Soc.*, 1948, **70**, 3135) in 88% yield. Diketen (89 g.) was added dropwise during 0·5 hr. to an agitated, boiling mixture of methyl mandelate (166 g.), benzene (200 c.c.), and triethylamine (1 c.c.) which was then refluxed for a further 0·5 hr. Removal of the solvent and crystallisation of the residue (250 g.) from benzene–light petroleum (b. p. 40—60°) gave the *acetoacetate* as needles, m. p. 56° (Found: C, 62·3; H, 5·4. $C_{13}H_{14}O_5$ requires C, 62·4; H 5·65%).

α-Acetyl-γ-phenyltetronic Acid (III; $R^1 = Ph$, $R^2 = H$).—To a warm agitated solution of the above ester (200 g.) in toluene (200 c.c.) small pieces of sodium (19 g.) were added. The vigorous initial reaction was moderated by external cooling, after which the mixture was refluxed for 3·5 hr., material (50 c.c.), b. p. 55—80°, being distilled off meanwhile. The product was acidified with concentrated hydrochloric acid (80 c.c.)–water (100 c.c.) and then extracted with benzene. Removal of the solvent and crystallisation of the residue (95 g., 54·5%) from ethyl acetate–light petroleum (b. p. 60—80°) gave the tetronic acid as pale yellow needles, m. p. 104—105° (Lecocq, *loc. cit.*, gives m. p. 104°) (Found: C, 65·85; H, 4·35. Calc. for $C_{12}H_{10}O_4$: C, 66·05; H, 4·6%).

The acid (2 g.) and phenylhydrazine (1·1 g.) in methanol gave the *phenylhydrazone*, which crystallised from methanol in needles, m. p. 157—158° (Found: N, 8·95. $C_{18}H_{16}O_3N_2$ requires N, 9·1%). The phenylhydrazone (1 g.) was heated with acetyl chloride (2 c.c.) in chloroform (20 c.c.) for 1 hr.; removal of solvents, trituration of the gummy residue with methanol, and crystallisation of the solid (0·8 g.) from chloroform-light petroleum (b. p. 60—80°) gave the *acetyl* derivative as needles, m. p. 197° (Found: N, 8·05. $C_{20}H_{18}O_4N_2$ requires N, 8·0%).

α-Acetyl-γ-phenyltetronic acid (1 g.), aniline (0·5 g.), and ethanol (10 c.c.) were refluxed for

5 min., part of the ethanol was then removed, and water was added. Crystallisation of the deposit from aqueous ethanol gave the *anilide* (XV; $R^1 = R^4 = Ph$, $R^2 = H$) as needles, m. p. 117° (Found: C, 73·7; H, 5·2; N, 4·5. $C_{18}H_{15}O_3N$ requires C, 73·7; H, 5·15; N, 4·8%).

Acetoacetate of Methyl α-Hydroxyisobutyrate (II; $R^1 = R^2 = R^3 = Me$).—Diketen (75 g.) was added during 0·5 hr. to methyl α-hydroxy*iso*butyrate (100 g.) and triethylamine (0·5 c.c.) at 60—70°, and the mixture heated at 70° for a further 0·5 hr. The product when distilled gave the *acetoacetate* (151 g., 88%), b. p. 118—125°/12 mm., n_D^{20} 1·4400 (Found: C, 53·6; H, 7·45. $C_9H_{14}O_5$ requires C, 53·45; H, 7·0%).

α-Acetyl-γγ-dimethyltetronic Acid (III; $R^1 = R^2 = Me$).—(*a*) Sodium (11·5 g.), in small pieces, was added to a warm, agitated solution of the above acetoacetate (101 g.) in toluene (150 c.c.). The reaction proceeded as previously described, and during isolation, a solid (57 g., 67%), m. p. 52—58°, was obtained on washing with cold light petroleum. Crystallisation from ether–light petroleum (b. p. 40—60°) gave the *tetronic acid* as pale yellow needles, m. p. 64—65°, b. p. 108—110°/12 mm. (Found: C, 56·45; H, 6·0. $C_8H_{10}O_4$ requires C, 56·45; H, 5·9%).

(*b*) A solution of the acetoacetate (46 g.) in toluene (25 c.c.) was added to one of sodium ethoxide (from 5·5 g. of sodium and 100 c.c. of ethanol), which was then refluxed for 4 hr. and set aside overnight. Most of the solvents were removed, and ether and concentrated hydrochloric acid (25 c.c.)–water (25 c.c.) were added. The solid residue (37 g., 98%), obtained with ether, was washed with light petroleum and then gave an almost pure product (35·5 g.), m. p. 58—59°. The *phenylhydrazone* crystallised from aqueous ethanol as prisms, m. p. 157·5—158° (Found: C, 64·95; H, 5·9; N, 10·5. $C_{14}H_{16}O_3N_2$ requires C, 64·6; H, 6·2; N, 10·75%).

The tetronic acid (1 g.) was warmed with ammonia solution (*d* 0·88; 2 c.c.) at 60° for 1 hr. and then set aside. The precipitated *amide* (XV; $R^1 = R^2 = Me$, $R^4 = H$), on crystallisation from water, gave needles, m. p. 181—182° (Found: C, 56·6; H, 6·65; N, 8·65. $C_8H_{11}O_3N$ requires C, 56·8; H, 6·55; N, 8·3%).

Acetoacetate of Methyl Benzilate (II; $R^1 = R^2 = Ph$, $R^3 = Me$).—Benzilic acid was esterified with methanol by Clinton and Laskowski's method (*loc. cit.*). To the ester (170 g.) in boiling benzene (200 c.c.) containing triethylamine (1 c.c.), diketen (61 g.) was added, with agitation, during 1 hr. After a further hour's refluxing, the solvent was removed and the residue (228 g.) crystallised twice from methanol, yielding the *acetoacetate* as needles, m. p. 91—92° (Found: C, 69·75; H, 5·45. $C_{19}H_{18}O_5$ requires C, 69·95; H, 5·55%).

α-Acetyl-γγ-diphenyltetronic Acid (III; $R^1 = R^2 = Ph$).—A mixture of sodium ethoxide solution (from 4·6 g. of sodium and 70 c.c. of ethanol) and the above acetoacetate (62 g.) in benzene (100 c.c.) was refluxed for 3 hr., set aside overnight, and then worked up as previously described. The product (52 g.; m. p. 90—95°) was washed with ether–light petroleum (b. p. 40—60°) and crystallised from *n*-butanol, giving the *tetronic acid* as a pale yellow solid, m. p. 102° (Found: C, 73·15; H, 5·0. $C_{18}H_{14}O_4$ requires C, 73·45; H, 4·8%). The phenylhydrazone was an oil, but a *semicarbazone* was obtained as needles, m. p. 186—188°, from ethyl acetate (Found: N, 11·9. $C_{19}H_{17}O_4N_3$ requires N, 11·95%).

The tetronic acid (1·47 g.) in ethanol (3 c.c.) was warmed with aqueous methylamine (40%; 1 c.c.). Addition of water gave a solid (1·2 g.) which, on recrystallisation from aqueous ethanol, gave the *amide* (XV; $R^1 = R^2 = Ph$, $R^4 = Me$) as needles, m. p. 182—183° (Found: C, 73·9; H, 5·25; N, 4·55. $C_{19}H_{17}O_3N$ requires C, 74·25; H, 5·55; N, 4·55%).

Acetoacetate of Methyl 1-Hydroxycyclohexanecarboxylate (II; $R^1R^2 = [CH_2]_5>$, $R^3 = Me$).—1-Hydroxy*cyclo*hexanecarboxylic acid was esterified by Clinton and Laskowski's method (*loc. cit.*). The methyl ester (118 g.), b. p. 68—72°/0·5 mm., n_D^{20} 1·4612, in boiling benzene (100 c.c.) and triethylamine (0·5 c.c.), was treated with diketen (65 g.) as previously described. The *acetoacetate* had b. p. 130—132°/1 mm., n_D^{20} 1·4683 (Found: C, 60·0; H, 7·5. $C_{12}H_{18}O_5$ requires C, 59·5; H, 7·5%).

α-Acetyl-γ-spirocyclohexanetetronic Acid (III; $R^1R^2 = [CH_2]_5>$).—The acetoacetate (74·5 g.) in benzene (100 c.c.) was added to sodium methoxide solution (from 7·0 g. of sodium and 100 c.c. of methanol), and the mixture refluxed for 4 hr. and set aside overnight. The product was concentrated, acidified, and extracted as previously described but with chloroform. Evaporation of the solvents and crystallisation of the yellow solid (63 g.), m. p. 108—115°, from methanol gave the *tetronic acid* (60 g., 95%) as white needles, m. p. 125—126° (Found: C, 62·85; H, 6·7. $C_{11}H_{14}O_4$ requires C, 62·75; H, 6·7%). The 2 : 4-*dinitrophenylhydrazone* crystallised in yellow needles, m. p. 195—196°, from ethanol (Found: C, 52·5; H, 4·75; N, 14·0. $C_{17}H_{18}O_7N_4$ requires C, 52·3; H, 4·65; N, 14·35%).

When a solution of the tetronic acid (1 g.) in aqueous methylamine (20%; 4 c.c.) was warmed, an oil was deposited which slowly crystallised. Recrystallisation from aqueous

methanol gave the *amide* (XV; $R^1R^2 = [CH_2]_5>$, $R^4 = Me$) as needles, m. p. 126° (Found: C, 64·3; H, 7·4; N, 6·55. $C_{12}H_{17}O_3N$ requires C, 64·55; H, 7·7; N, 6·3%).

The reaction of the tetronic acid (2·1 g.) in hot methanol (10 c.c.) with diethylamine (1 c.c.) afforded the *diethylamine* salt as needles, m. p. 180—181°, from ethanol (Found: C, 63·7; H, 8·95; N, 4·7. $C_{15}H_{25}O_4N$ requires C, 63·6; H, 8·9; N, 4·95%). The salt dissolved in water, and an immediate precipitate of the tetronic acid was obtained on addition of dilute hydrochloric acid.

Acetoacetate of Methyl 2-Hydroxy-1-phenylpropane-1-carboxylate (II; $R^1 = CH_2Ph$, $R^2 = R^3 = Me$).—*Methyl 2-hydroxy-1-phenylpropane-2-carboxylate* (I; $R^1 = CH_2Ph$, $R^2 = R^3 = Me$) was prepared from the acid in 58% yield; it had b. p. 84—87°/3 mm., n_D^{20} 1·5080 (Found: C, 68·45; H, 7·3. $C_{11}H_{14}O_3$ requires C, 68·05; H, 7·1%). Diketen (19·5 g.) was added to a refluxing solution of the ester (42·2 g.) in benzene (100 c.c.) containing triethylamine (0·5 c.c.). The *acetoacetate* was obtained as a pale yellow oil (43·7 g., 72·5%), b. p. 144—150°/1·5 mm., n_D^{20} 1·5047 (Found: C, 65·0; H, 6·5. $C_{15}H_{18}O_5$ requires C, 64·75; H, 6·5%).

α-Acetyl-γ-benzyl-γ-methyltetronic Acid (III; $R^1 = CH_2Ph$, $R^2 = Me$).—The acetoacetate (40·7 g.) in benzene (50 c.c.) was refluxed with sodium ethoxide solution (from 3·5 g. of sodium and 50 c.c. of ethanol) for 4 hr. After acidification of the solution and isolation of the product with ether, an oil was obtained that crystallised when rubbed with light petroleum. Crystallisation of the solid (30 g., 89%) from aqueous methanol gave the *tetronic acid* as pale yellow needles, m. p. 92—93° (Found: C, 68·45; H, 5·9. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·75%).

A solution of the acid (1 g.) in methanol (10 c.c.) was refluxed with *p*-toluidine (0·6 g.) for 0·5 hr. Addition of water and cooling precipitated the *toluidide* (XV; $R^1 = PhCH_2$, $R^2 = Me$, $R^3 = p\text{-}MeC_6H_4$), which formed needles (from aqueous methanol), m. p. 143° (Found: C, 75·3; H, 6·25; N, 4·2. $C_{21}H_{21}O_3N$ requires C, 75·2; H, 6·3; N, 4·2%).

Bromination of α-Acetyltetronic Acids.—[Unless otherwise stated these bromo-compounds were crystallised from ethyl acetate–light petroleum (b. p. 60—80°).] (a) *α-Bromoacetyl-γ-methyltetronic acid* (IX). To a solution of α-acetyl-γ-methyltetronic acid (1·56 g.) in acetic acid (5 c.c.) at 40° a solution of bromine in acetic acid (1M; 10 c.c.) was added during 1 hr. Evaporation *in vacuo* and washing with ether–light petroleum (b. p. 40—60°) gave a solid (1·4 g., 60%), from which the *bromo*-compound (IX) was obtained as pale yellow needles, m. p. 135° (decomp.) (Found: C, 36·0; H, 3·3; Br, 33·7. $C_7H_7O_4Br$ requires C, 35·8; H, 3·0; Br, 34·0%).

(b) *α-Bromo-γ-methyltetronic acid* (X). After the addition of 1 mol. of bromine as described above, water (10 c.c.) and more bromine solution (1M; 10 c.c.) at 20° were added. Evaporation as above at 30° and crystallisation gave (±)-α-bromo-γ-methyltetronic acid (1·0 g., 52%) as prisms, m. p. 172° [Raistrick *et al.*, *loc. cit.*, give m. p. 172° for (+)-α-bromo-γ-methyltetronic acid].

(c) *α-Bromo-γγ-dimethyltetronic acid* (XI). Bromine in acetic acid (1M; 10 c.c.) was added dropwise during 0·5 hr. to a solution of α-acetyl-γγ-dimethyltetronic acid (1·7 g.) in acetic acid (5 c.c.) at 30°. Water (10 c.c.) was added followed by more bromine solution (1M; 10 c.c.) at 20°. The resulting solution was evaporated *in vacuo*, and the product (1·7 g.), m. p. 173—178°, crystallised, giving the *bromo-tetronic acid* as prisms, m. p. 186—187°, soluble in sodium hydrogen carbonate solution and giving a red colour with ferric chloride solution (Found: C, 34·95; H, 3·2; Br, 38·5. $C_6H_7O_3Br$ requires C, 34·8; H, 3·4; Br, 38·6%). A solution of the bromotetronic acid (2·07 g.) in methanol (10 c.c.) and barium hydroxide solution (0·2N; 50 c.c.) was agitated with palladium–charcoal (0·2 g.; 3% Pd) in an atmosphere of hydrogen (uptake: 254 c.c. at 21°/771 mm. in 30 min. Theory 238 c.c.). After filtration and evaporation of the solution, the solid residue was extracted with ethyl acetate to give γγ-dimethyltetronic acid (XII), which crystallised from ethyl acetate–light petroleum (b. p. 60—80°) as prismatic needles (0·9 g.), m. p. 142—143° (Benary, *Ber.*, 1907, **40**, 1082, gives m. p. 142—143°).

(d) *α-Bromo-γ-spirocyclohexanetetronic acid* (XIII). α-Acetyl-γ-*spirocyclo*hexanetetronic acid (2·1 g.) was brominated as described in (c). Evaporation gave the *bromo-tetronic acid* (3·7 g.) which crystallised from ethyl acetate as prisms, m. p. 216—217°, soluble in sodium hydrogen carbonate solution and giving a red colour with ferric chloride solution (Found: C, 43·95; H, 4·3; Br, 32·3. $C_9H_{11}O_3Br$ requires C, 43·75; H, 4·5; Br, 32·35%). Hydrogenation of the bromo-tetronic acid (2·47 g.), as described in (c), resulted in the absorption of 240 c.c. of gas at 20°/770 mm. (theory, 237 c.c.) in 50 min. Isolation as above afforded *γ-spirocyclo*hexanetetronic acid (XIV) (1·2 g.) as prisms, m. p. 198—199°, from ethyl acetate (Jones and Whiting, *J.*, 1949, 1421, give m. p. 198°).

Hydrolysis of α-Acetyltetronic Acids.—(a) *α-Acetyl-γ-methyltetronic acid.* The acid (5 g.) was dissolved in aqueous sodium hydroxide (3 g. in 5 c.c.) with cooling and, after 1 hr. at room

temperature, the solution was heated at 50° for 3 hr. After acidification and isolation with ether, an oil was obtained which crystallised when rubbed with aqueous methanol and was recrystallised from the same solvent. γ-Methyltetronic acid (0·15 g.) formed needles, m. p. 116—117° (Benary, *Ber.*, 1911, **44**, 1763, gives m. p. 117—119°).

(b) *α-Acetyl-γγ-diphenyltetronic acid.* A solution of the acid (2·94 g.) in sodium hydroxide solution (5%; 16 c.c.) was set aside at room temperature for 6 hr.: after 2 hr., deposition of solid commenced. Acidification afforded a yellow solid (2·0 g.) which, after two crystallisations from aqueous methanol, gave γγ-diphenyltetronic acid (1·6 g.) as pale yellow needles, m. p. 213° (Lecocq, *Compt. rend.*, 1946, **222**, 299, gives m. p. 212°) (Found: C, 76·0; H, 4·75. Calc. for $C_{16}H_{12}O_3$: C, 76·15; H, 4·8%).

BRITISH INDUSTRIAL SOLVENTS, DEVELOPMENT DEPT.,
HEDON, HULL.

[*Received, August 1st*, 1953.]

Derivatives of Acetoacetic Acid. Part V. The Reaction of Diketen with Thioureas, Amidines, Guanidines, and S-Substituted Thioureas.†*

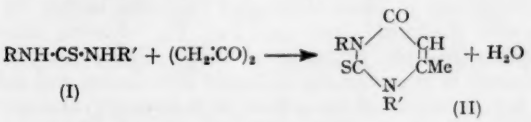
By R. N. LACEY.

[Reprint Order No. 4548.]

The reaction of diketen with thioureas, in general, gave substituted thiouracils, although *NN'*-diphenylthiourea afforded only phenyl *iso*thiocyanate and acetoacetanilide. Acetamidine and benzamidine with diketen gave the same pyrimidones as are obtained by using acetoacetic ester. Guanidine and methylguanidine gave the known aminopyrimidones but *NN'*-diphenylguanidine gave a 1 : 3-oxazine. The condensation of *S*-alkylthioureas proceeded *via* a 1 : 3-oxazine which, with alkali, rearranges with loss of water to give a 2-alkylthiopyrimidone.

WHILE the formation of pyrimidine derivatives from the reaction of an acetoacetic ester with urea and its derivatives, *e.g.*, ureas, thioureas, guanidines, and *iso*thioureas, and with amidines, has long been known, little attention has been devoted to the reaction of diketen, which affords a valuable precursor of acetoacetic esters, with these compounds. Boese (U.S.P. 2,138,756/1938) has shown that urea and alkyl-ureas with diketen in dioxan give substituted uracils. The yield of 6-methyluracil obtained was poor and most of the diketen was converted into dehydroacetic acid, acetone, etc., the latter arising from the hydrolysis of diketen by the water eliminated.

The condensation of diketen with amines of basic strength not less than that of aniline occurs in aqueous medium but diketen did not react with thiourea in water, rapid hydrolysis of the diketen or, under milder conditions, recovery of the starting materials taking place. No perceptible reaction took place in benzene, in which thiourea is only slightly soluble, but vigorous reaction occurred in boiling acetic acid with the formation of 6-methyl-2-thiouracil (II; R = R' = H) in 55% yield.



Similarly, methylthiourea and diketen in boiling acetic acid give a 30% yield of crystalline product, shown, by hydrolysis with concentrated hydrochloric acid at 160—170° to 1 : 6-dimethyluracil, to be essentially 1 : 6-dimethyl-2-thiouracil.

Phenylthiourea with diketen in boiling acetic acid gave 6-methyl-3-phenyl-2-thiouracil (II; R = Ph, R' = H), the configuration being proved by comparison with an authentic specimen obtained from the reaction of phenyl *iso*thiocyanate with methyl β-aminocrotonate (Behrend, Meyer, and Buchholz, *Annalen*, 1901, **314**, 224). The solubility of

* Part IV, preceding paper. † Patents pending: B.P. Appln. 29158/1950, 29159/1950.

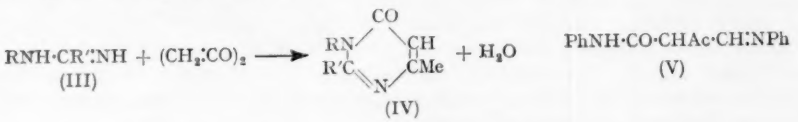
phenylthiourea permitted the reaction with diketen to be carried out in several other solvents.

NN'-Diethylthiourea was also successfully condensed with diketen to give 1 : 3-diethyl-6-methyl-2-thiouracil (II; R = R' = Et). However, *NN'*-diphenylthiourea gave phenyl *iso*thiocyanate, acetoacetanilide, and a small amount of *NN'*-diphenylurea, arising from the cleavage of the thiourea molecule. Similarly, *NN'*-di-*o*-tolylthiourea gave acetoacet-*o*-toluidide. Similar cleavage of *NN'*-diphenylthiourea by acetic anhydride has been observed by Hugershoff (*Ber.*, 1899, **32**, 3655; cf. Werner, *J.*, 1891, 396).

$$PhNH{\cdot}CS{\cdot}NHPh + (CH_2{:}CO)_2 \longrightarrow PhNCS + PhNH{\cdot}CO{\cdot}CH_2Ac$$

The reaction of *N*-methyl-*N'*-phenylthiourea in boiling acetic acid gave a thiouracil for which two possible configurations (II; R = Ph, R' = Me or R = Me, R' = Ph) may be postulated. Acid hydrolysis of the thiouracil gave the corresponding uracil, which was prepared unambiguously by the methylation of 6-methyl-3-phenyluracil, indicating structure (II; R = Ph, R' = Me) for the thiouracil.

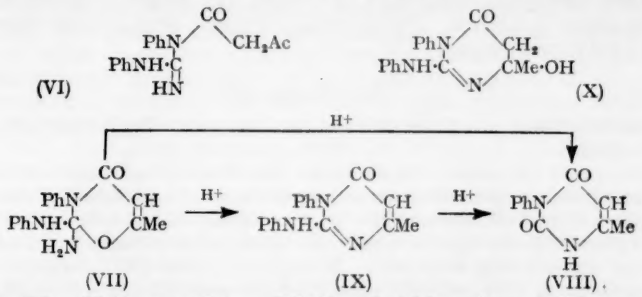
Pinner has shown the reaction of acetoacetic ester with amidines to afford a general route to substituted 4-hydroxypyrimidines (cf. Pinner, *Ber.*, 1884, **17**, 2520). The reaction of acetamidine, liberated from its hydrochloride with sodium hydroxide, in aqueous solution with diketen at 0° afforded only an unidentifiable gum. However, the use of alcoholic sodium ethoxide to liberate the free base gave 3 : 4-dihydro-2 : 6-dimethyl-4-oxopyrimidine. Since the reaction of diketen under these conditions was much more rapid than its reaction with alcohol, it is concluded that the diketen reacted with the amidine without intermediate formation of an acetoacetic ester, and that failure to obtain the pyrimidone by reaction in the presence of water must be attributed to the rapid hydrolysis of acetamidine. Benzamidine, whether as the free base or as liberated *in situ* from its hydrochloride, readily reacted with diketen in water at 10—13° to give 3 : 4-dihydro-6-methyl-4-oxo-2-phenylpyrimidine (IV; R = H, R' = Ph) in high yield. *NN'*-Diphenylformamidine did not give a pyrimidine derivative but yielded α-(phenyliminomethyl)acetoacetanilide (V), previously obtained by Dains (*Ber.*, 1902, **35**, 2509) from the reaction of this amidine with ethyl acetoacetate.



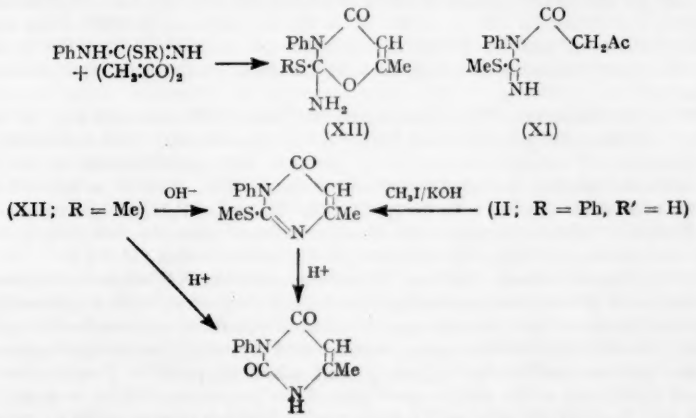
Guanidine, liberated *in situ* in aqueous solution, readily reacted with diketen at room temperature to give 2-amino-3 : 4-dihydro-6-methyl-4-oxopyrimidine (IV; R = H, R' = NH_2); methylguanidine reacted similarly to give (IV; R = Me, R' = NH_2). *NN'*-Diphenylguanidine (III; R = Ph, R' = NHPh) is readily obtainable as a stable free base; its rapid reaction with diketen in acetone solution at room temperature gave an almost quantitative yield of a non-ketonic solid which gave analytical data corresponding to $C_{17}H_{17}O_2N_3$. Its insolubility in alkali eliminated (VI), and largely by analogy with the reaction of diketen with *S*-alkylthioureas (see Part VI, following paper), the product is regarded as a 2 : 3-dihydro-4-oxo-1 : 3-oxazine (VII). The evidence afforded by light-absorption measurements is in agreement with this formulation and sufficed to eliminate (X), which would not be expected to exhibit high-intensity absorption in the 2100—3500-Å region (contrast Gage, *J.*, 1949, 221). Prolonged refluxing with dilute hydrochloric acid gave 6-methyl-3-phenyluracil (VIII), while hydrolysis with weaker acid and for a shorter time afforded a product, formulated as 2-anilino-3 : 4-dihydro-6-methyl-4-oxo-3-phenylpyrimidine (IX), since further hydrolysis with hydrochloric acid gave 6-methyl-3-phenyluracil and aniline. Curd, Raison, and Rose (*J.*, 1946, 362) have shown that 3 : 4-dihydro-6-methyl-2-methylthio-4-oxopyrimidine (IV; R = H, R' = MeS) when heated with aromatic amines affords the corresponding 2-arylamino-compounds (IV; R = H, R' = ArNH), with the elimination of methanethiol. However, attempts to use this method to synthesise (IX) from aniline and 3 : 4-dihydro-6-methyl-2-methylthio-

4-oxo-3-phenylpyrimidine (IV; R = Ph, R′ = MeS) were unsuccessful and it is likely that the reaction is limited to compounds unsubstituted in the 3-position which can enolise.

A rapid reaction took place in the cold between diketen and a solution of *S*-methylthiuronium iodide and one equivalent of aqueous sodium hydroxide. However, only after two days was crystallisation of 3 : 4-dihydro-6-methyl-2-methylthio-4-oxopyrimidine



(IV; R = H, R′ = MeS) complete. *NS*-Dimethylthiuronium iodide was similarly treated with aqueous sodium hydroxide and diketen, but even after being left overnight no precipitation had occurred. However, on addition of more aqueous sodium hydroxide, crystallisation of 3 : 4-dihydro-3 : 6-dimethyl-2-methylthio-4-oxopyrimidine (IV; R = Me, R′ = MeS) (cf. Wheeler and McFarland, *Amer. Chem. J.*, 1909, **42**, 105) ensued within a few minutes. These experiments had indicated that diketen reacted rapidly with the two *S*-alkylthioureas to give intermediates which were converted slowly, or more rapidly in the presence of alkali, into pyrimidones. This hypothesis received powerful support when the reaction of *S*-methyl-*N*-phenylthiourea (III; R = Ph, R′ = MeS) with diketen was studied. In this case the stability of the free base allowed the condensation to be carried out in ether, and, after a rapid exothermic reaction, a solid crystallised. Analysis of the product indicated the empirical formula of the expected pyrimidone plus water, but when the product was treated with aqueous alkali, there was rapid precipitation of 3 : 4-dihydro-6-methyl-2-methylthio-4-oxo-3-phenylpyrimidine (IV; R = Ph, R′ = MeS). The configuration of this pyrimidone was established both by methylation of 6-methyl-3-phenyl-2-thiouracil (II; R = Ph, R′ = H) and by acid hydrolysis to 6-methyl-3-phenyluracil. The intermediate was soluble in acids but since it was insoluble in alkali and



non-ketonic, (XI) must be eliminated. The product is probably a 1 : 3-oxazine derivative (XII; R = Me), this formulation being supported by light-absorption evidence ($\lambda_{max.}$ 2220 Å).

S-Benzyl-*N*-methylthiourea readily reacted with diketen to give a 1 : 3-oxazine derivative (XII; R = CH_2Ph); the formulation again being confirmed by light-absorption measurements, which showed an intense band at $\lambda_{max.}$ 2230 Å. Although alkali failed to convert the product into a 2-benzylthio-3 : 4-dihydro-4-oxopyrimidine, acid hydrolysis gave 6-methyl-3-phenyluracil and toluene-ω-thiol.

While 1 : 3-benzoxazines, derived from urea and salicylic acid derivatives, have frequently been described, compounds containing the simple 1 : 3-oxazine ring system appear to be almost unknown. Further examples, also derived from diketen, are to be discussed in a subsequent paper.

Experimental

M. p.s were determined on a Kofler block and are corrected. Light-absorption measurements were made in ethanol.

Condensations with Thioureas.—(a) *Thiourea.* No reaction took place between diketen and thiourea in an aqueous suspension at room temperature. To a solution of thiourea (19 g.) in acetic acid (50 c.c.) at 110° diketen (22·5 g.) was rapidly added with agitation: a vigorous reaction took place with the deposition of solid. After being refluxed for 15 min., the product was cooled and a pale yellow solid (20 g., 55·5%), m. p. 280—290° (decomp.), was collected; it did not depress the m. p. of authentic 6-methyl-2-thiouracil (II; R = R′ = H). Methylation with an excess of alcoholic potassium hydroxide and methyl iodide gave 3 : 4-dihydro-3 : 6-dimethyl-2-methylthio-4-oxopyrimidine, m. p. and mixed m. p. 94° (Wheeler and McFarland, *loc. cit.*, give m. p. 94°). Distillation of the filtrate from the above diketen condensation gave acetone (3 g.) followed by a fraction, b. p. 60—100°, which had a powerful sulphurous odour: the presence of thioketones was suspected.

(b) *Methylthiourea.* Diketen (8·6 g.) was added during 15 min. to a refluxing, agitated solution of methylthiourea (9·0 g.) in acetic acid (25 c.c.), and refluxing continued for a further 20 min. Water was added; the product (4·6 g.), m. p. 235—245° could not be purified to a sharp melting point by repeated crystallisation. A portion (1 g.) was heated with concentrated hydrochloric acid (10 c.c.) in a sealed tube at 160—170° for 20 hr. Concentration gave a precipitate which on recrystallisation from water formed prisms, m. p. 224—225°, undepressed with authentic 1 : 6-dimethyluracil (Behrend and Thurm, *Annalen*, 1902, **323**, 160, give m. p. 219—220°).

(c) *Phenylthiourea.* Diketen (23 g.) was added during 0·5 hr. to a refluxing, agitated solution of phenylthiourea (38 g.) in acetic acid (100 c.c.), and heating continued for a further 0·5 hr. Part of the solvent was then distilled off, and water added. The precipitate was recrystallised from aqueous acetic acid, giving 6-methyl-3-phenyl-2-thiouracil (28 g., 47·5%), m. p. and mixed m. p. 266°. The authentic sample was prepared by heating phenyl *iso*thiocyanate (13·5 g.) and methyl β-aminocrotonate (11·5 g.) at 150° for 3 hr. Crystallisation of the product gave the thiouracil (II; R = Ph, R′ = H) as plates, m. p. 266°, from aqueous acetic acid (Behrend, Meyer, and Buchholz, *loc. cit.*, give m. p. 255—256°). The condensation of diketen with phenylthiourea in ethyl acetate, benzene, chloroform, and dioxan gave very similar results.

(d) NN′-*Diethylthiourea.* To a solution of *NN*′-diethylthiourea (13·2 g.) in boiling acetic acid (20 c.c.) diketen (8·6 g.) was added during 0·5 hr., and heating then continued for a further 0·5 hr. Removal of solvent under reduced pressure and crystallisation of the residue from aqueous methanol gave 1 : 3-*diethyl*-6-*methyl*-2-*thiouracil* (II; R = R′ = Et) (13·5 g., 63%) as needles, m. p. 97—98° (Found: C, 54·7; H, 6·8; N, 14·1. $C_9H_{14}ON_2S$ requires C, 54·5; H, 7·1; N, 14·15%). Similar preparations in other solvent gave the following yields: benzene (11·5 g.), chloroform (10·0 g.), ethyl acetate (11·0 g.), and dioxan (11·5 g.).

(e) NN′-*Diphenylthiourea.* Diketen (7·5 g.) was added to *NN*′-diphenylthiourea (19·5 g.) in boiling acetic acid (20 c.c.) as described for the diethyl compound. After removal of the solvent under reduced pressure, the product was dissolved in ether and extracted with aqueous sodium hydroxide. Acidification of the aqueous extract and crystallisation of the deposited solid from water, gave acetoacetanilide (9·6 g.), m. p. and mixed m. p. 85°. Evaporation of the ether extract and distillation of the residue gave phenyl *iso*thiocyanate (4·2 g.), b. p. 90—93°/10 mm., n_D^{20} 1·6438 (lit., b. p. 95°/12 mm., $n_D^{23\cdot4}$ 1·6492), and *NN*′-diphenylurea (0·15 g.), m. p. and mixed m. p. 235°.

A similar experiment with *NN*′-di-*o*-tolylthiourea (12·8 g.), diketen (4·5 g.), and acetic acid (40 c.c.) gave acetoacet-*o*-toluidide, m. p. and mixed m. p. 104°.

(f) N-*Methyl*-N′-*phenylthiourea.* *N*-Methyl-*N*′-phenylthiourea was prepared in quantitative yield from phenyl *iso*thiocyanate and aqueous methylamine (40%) at 60—100°. Diketen (13·3 g.) was added during 10 min. to a refluxing agitated solution of the thiourea (25 g.) in acetic acid (50 c.c.), and heating continued for a further 15 min. Removal of 30 c.c. of solvent, addition of water, and crystallisation of the deposited solid (23·5 g.) from *n*-butanol gave 1 : 6-*dimethyl*-3-*phenyl*-2-*thiouracil* (II; R = Ph, R′ = Me) as prisms, m. p. 197—199° (Found: C, 62·4; H, 5·25. $C_{12}H_{12}ON_2S$ requires C, 62·05; H, 5·2%).

The thiouracil (3 g.) was heated with concentrated hydrochloric acid (10 c.c.) in a sealed tube at 160° overnight. The product, smelling strongly of hydrogen sulphide, was evaporated giving a solid (1·0 g.) which crystallised from ethyl acetate as needles, m. p. 211°. The same compound was prepared by refluxing 4-methyl-1-phenylthiouracil (II; R = Ph, R′ = H; 0·5 g.) with an excess of alcoholic potassium hydroxide (0·5N; 10 c.c.) and methyl iodide (2 g.) for 1·5 hr. 1 : 6-*Dimethyl*-3-*phenyluracil* formed needles, m. p. 211°, from ethyl acetate (Found: C, 66·95; H, 5·75. $C_{12}H_{12}O_2N_2$ requires C, 66·65; H, 5·6%). A mixed m. p. determination with the material prepared as above showed no depression.

Condensations with Amidines.—(a) *Acetamidine.* A solution of acetamidine hydrochloride (18·9 g.) in ethanol (100 c.c.) was added to one of sodium ethoxide (from 4·6 g. of sodium and 60 c.c. of ethanol), and diketen (17·5 g.) was added dropwise with agitation to the cooled mixture (0—5°) during 0·5 hr. After 5 days, the solution was filtered and evaporated, giving 3 : 4-dihydro-3 : 6-dimethyl-4-oxopyrimidine (IV; R = H, R′ = Me) (8·6 g., 34·5%), m. p. 193° (Pinner, *loc. cit.*, gives m. p. 192°).

(b) *Benzamidine.* Diketen (8·9 g.) was added to a solution of benzamidine hydrochloride dihydrate (19·25 g.) in aqueous sodium hydroxide (10%; 40 c.c.) at 10—13°. After 0·5 hr. at room temperature, the pale yellow, crystalline deposit of 3 : 4-dihydro-6-methyl-4-oxo-2-phenylpyrimidine (IV; R = H, R′ = Ph) (12 g., 64·5%), m. p. 214°, was collected. A similar experiment, in which diketen reacted with an aqueous solution of the previously isolated free base, gave a 70% yield of the pyrimidone, m. p. 215° (Pinner, *loc. cit.*, gives m. p. 216°).

(c) NN′-*Diphenylformamidine.* Diketen (4·4 g.) was added during 20 min. to an agitated solution of *NN*′-diphenylformamidine (9·8 g.) in benzene (50 c.c.) at 50—60°. After the solution had refluxed for 20 min. solvent was distilled off and the residue crystallised from aqueous methanol, giving β-phenyliminomethylacetoacetanilide (V) (9·8 g.) as needles, m. p. 156° (Dains, *loc. cit.*, gives m. p. 156°).

Condensations with Guanidines.—(a) *Guanidine.* Aqueous sodium hydroxide (8 g. in 25 c.c.) was added to an agitated suspension of guanidine carbonate (18 g.) in water (25 c.c.). Diketen (17·5 g.) was added to the pale yellow solution during 30 min. at 15—20°, and the product was stirred at room temperature for 1 hr., giving 2-amino-3 : 4-dihydro-6-methyl-4-oxopyrimidine (IV; R = H, R′ = NH_2) (3·5 g., 14%), m. p. 285° (decomp.). In a similar experiment with guanidine hydrochloride (19 g.), a 28% yield of the aminopyrimidone, m. p. 285—290° (decomp.), was obtained [Gabriel and Colman, *Ber.*, 1899, **32**, 2924, give m. p. 297—299° (decomp.), on rapid heating].

(b) *Methylguanidine.* Diketen (8·8 g.) was added during 0·5 hr. to a solution of methylguanidine hydrochloride (11 g.) and sodium hydroxide (4 g.) in water (60 c.c.) at 0—10°. The solution was set aside overnight, then concentrated under reduced pressure, and cooled. Sodium chloride was first precipitated, followed by 2-amino-3 : 4-dihydro-3 : 6-dimethyl-4-oxopyrimidine (IV; R = Me, R′ = NH_2) (1·1 g., 8%), m. p. and mixed m. p. 310° (Majima, *Ber.*, 1908, **41**, 176, gives m. p. 312°).

(c) NN′-*Diphenylguanidine.* Diketen (8·6 g.) was added to a solution of *NN*′-diphenylguanidine (21·1 g.) in acetone (50 c.c.) during 20 min., initially at 20°. After a further 15 min.' stirring, the solution was evaporated under reduced pressure to give a white solid (29 g., 98%), m. p. 99—102° (decomp.). Crystallisation from acetone–light petroleum (b. p. 60—80°) gave 2-*amino*-2-*anilino*-2 : 3-*dihydro*-6-*methyl*-4-*oxo*-3-*phenyl*-1 : 3-*oxazine* (VII) as prisms, m. p. 114° (decomp.) (Found: C, 69·05; H, 5·6; N, 14·4. $C_{17}H_{17}O_2N_3$ requires C, 69·2; H, 5·8; N, 14·3%). Light absorption: end absorption, 2100 Å; ε, 14,000: inflection, 3000 Å; ε, 2800. The compound was soluble in dilute hydrochloric acid but insoluble in aqueous sodium hydroxide with which it afforded an oil on being boiled. No reaction occurred with 2 : 4-dinitrophenylhydrazine sulphate.

The oxazine (5 g.) was refluxed with concentrated hydrochloric acid (5 c.c.) and water (12 c.c.) for 2 hr. Cooling and neutralisation of the solution precipitated a solid (2·0 g.), which, on crystallisation, afforded 2-*anilino*-3 : 4-*dihydro*-6-*methyl*-4-*oxo*-3-*phenylpyrimidine* (IV; R = Ph, R′ = PhNH) as needles, m. p. 113—114° (Found: C, 73·85; H, 5·55; N, 14·9. $C_{17}H_{15}ON_3$

requires C, 73·55; H, 5·45; N, 15·15%). Hydrolysis with a higher concentration of acid (7 c.c. of concentrated acid plus 8 c.c. of water) and refluxing for 4 hr. gave 6-methyl-3-phenyluracil (crude yield: 3·1 g.), m. p. and mixed m. p. 256° (from water) [Behrend, Meyer, and Buchholz, *loc. cit.*, give m. p. 244—245° (decomp.)].

Condensations with S-Substituted Thioureas.—(a) *S-Methylthiourea.* Diketen (22 g.) was added dropwise to an agitated, cooled (<5°) solution of *S*-methylthiuronium iodide (55 g.) in aqueous sodium hydroxide (10%; 100 c.c.). After 2 days, 3 : 4-dihydro-6-methyl-2-methylthio-4-oxopyrimidine (IV; R = H, R′ = MeS) (24·6 g., 70%), m. p. 221°, was collected (Wheeler and Merriam, *Amer. Chem. J.*, 1903, **29**, 492, give m. p. 219°).

(b) NS-*Dimethylthiourea.* Diketen (4·3 g.) was added as in (a) to a solution of *NS*-dimethylthiuronium iodide (11·6 g.) in aqueous sodium hydroxide (1N; 50 c.c.) during 0·5 hr. Next day more aqueous sodium hydroxide (10%; 15 c.c.), was added and the precipitate (2·6 g., 31%) of 3 : 4-dihydro-3 : 6-dimethyl-2-methylthio-4-oxopyrimidine, (IV; R = Me, R′ = MeS), m. p. 90°, was recrystallised from water, giving needles, m. p. and mixed 94° (Wheeler and McFarland, *loc. cit.*, give m. p. 94°).

(c) S-*Methyl*-N-*phenylthiourea.* *S*-Methyl-*N*-phenylthiourea (16·7 g.) in ether (150 c.c.) was treated with diketen (8·6 g.), added to the agitated solution during 0·5 hr. A white powder (16·1 g.), m. p. 109° (decomp.) slowly crystallised, and concentration of the liquid gave a further crop (2·9 g., total yield 75·5%), m. p. 101—108° (decomp.). 2-*Amino*-2 : 3-*dihydro*-6-*methyl*-2-*methylthio*-4-*oxo*-3-*phenyl*-1 : 3-*oxazine* (XII; R = Me) formed small crystalline granules, m. p. 118° (decomp.), from ethyl acetate (Found: C, 57·55; H, 5·35; N, 11·2. $C_{12}H_{14}O_2N_2S$ requires C, 57·6; H, 5·65; N, 11·2%). Light absorption: max., 2220 Å; ε, 14,700: inflection, 2700 Å; ε = 2500 [β-methoxycrotonic acid has max., 2340 Å (ε, 14,000), cf. Braude, *Ann. Reports*, 1945, **42**, 119]. Ethanol, acetone, and ethyl acetate were also successfully used as reaction solvents.

This product (0·5 g.) was warmed with methanol (5 c.c.), water (5 c.c.), and aqueous potassium hydroxide (0·5N; 0·5 c.c.); the solid precipitate (0·45 g.), m. p. 146°, was crystallised from aqueous methanol, giving 3 : 4-*dihydro*-6-*methyl*-2-*methylthio*-4-*oxo*-3-*phenylpyrimidine* (IV; R = Ph, R′ = MeS) as rhombic crystals, m. p. 147° (Found: C, 62·05; H, 5·05; N, 12·0. $C_{12}H_{12}ON_2S$ requires C, 62·05; H, 5·2; N, 12·05%). Potassium hydroxide was replaced by barium hydroxide, pyridine, and triethylamine, though not by sodium carbonate, with similar results. A specimen was also prepared by heating 6-methyl-3-phenyl-2-thiouracil (1·0 g.), methyl iodide (1·0 g.) and alcoholic potassium hydroxide (0·5N; 10 c.c.) under reflux for 1 hr. Addition of water and cooling gave a crystalline precipitate (0·7 g.), m. p. 147°, undepressed with the above material.

The oxazine (XII; R = Me) (2·0 g.) was refluxed with concentrated hydrochloric acid (20 c.c.) for 2 hr. methanethiol was evolved and, on cooling, a white precipitate, m. p. 251°, was deposited. Crystallisation from water gave 6-methyl-3-phenyluracil, m. p. and mixed 258—259° [Behrend, Meyer, and Buchholz, *loc. cit.*, give m. p. 244—245° (decomp.)]. On heating of the oxazine (XII; R = Me) (5·0 g.) in an oil-bath at 130—140° for 1 hr., methanethiol was evolved, and repeated crystallisation from water of the gummy solid that remained gave 6-methyl-3-phenyluracil (0·6 g.), m. p. and mixed m. p. 255—257°.

(d) S-*Benzyl*-N-*phenylthiourea.* Diketen (4·2 g.) was added during 15 min. to a solution of *S*-benzyl-*N*-phenylthiourea (12·1 g.; m. p. 80°) in ether (70 c.c.). Evaporation, after decantation from a little separated solid, gave a white crystalline residue (14·7 g.), m. p. 110—112°. Crystallisation from ethyl acetate–light petroleum (b. p. 60—80°) gave 2-*amino*-2-*benzylthio*-3 : 4-*dihydro*-6-*methyl*-4-*oxo*-3-*phenyl*-1 : 3-*oxazine* (XII; R = CH_2Ph) as needles, m. p. 114° (decomp.) (Found: C, 66·0; H, 5·4; N, 8·6. $C_{18}H_{18}O_2N_2S$ requires C, 66·25; H, 5·55; N, 8·6%). Light absorption: max. 2230 Å; ε, 22,600.

The oxazine (3·5 g.) was refluxed with concentrated hydrochloric acid (20 c.c.) for 1 hr., and the toluene-ω-thiol formed was steam-distilled. On cooling the residue, 6-methyl-3-phenyluracil (1·6 g.), m. p. and mixed m. p. 255—256° was deposited.

BRITISH INDUSTRIAL SOLVENTS, DEVELOPMENT DEPT.,
HEDON, HULL.

[*Received, August 1st*, 1953.]

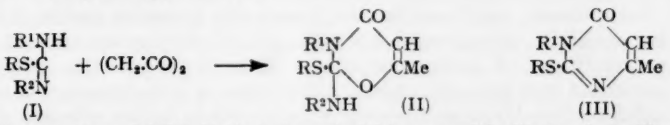
Derivatives of Acetoacetic Acid. Part VI. A Synthesis of 1 : 3-Oxazine Derivatives employing Diketen.†*

By R. N. Lacey.

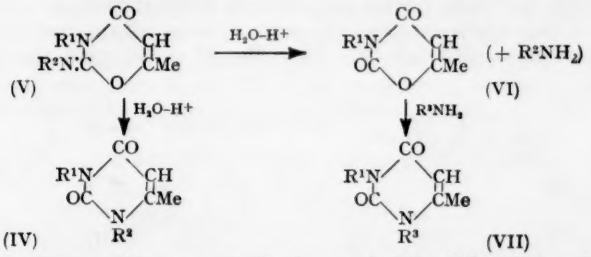
[Reprint Order No. 4549.]

Diketen reacts with *NN'*-disubstituted derivatives of *S*-alkylthiourea to give 2-imino-1 : 3-oxazine derivatives with the elimination of thiol. The reaction is general, and the substituents may be alkyl, aryl, or aralkyl. Acid hydrolysis of the products gives dihydro-2 : 4-dioxo-1 : 3-oxazines, with elimination of amine, and, in certain cases, uracils, arising from the rearrangement of the imino-oxazine. The dihydro-dioxo-1 : 3-oxazines react with ammonia and with alkyl- and aralkyl-amines to give substituted uracils, affording a new route of wide applicability to these compounds.

In Part V *, it was shown that reaction of diketen with *S*-alkylthioureas (I; R^1 = H, Ph, or Me, R^2 = H) does not directly afford the pyrimidones expected by analogy with the well-known reaction of *S*-alkylthioureas and acetoacetic esters, but gives dihydro-1 : 3-oxazines (II), from which the pyrimidones (III) are obtained by treatment with basic catalysts. It was expected that *NN'*-disubstituted *S*-alkylthioureas with diketen might afford 1 : 3-oxazines (an almost unknown ring system), although they would not be convertible into 2-(alkylthio)pyrimidones.



However, the reaction of *NN'*-diethyl-*S*-methylthiourea with diketen in boiling benzene was accompanied by the elimination of methanethiol. Analysis showed the product, m. p. 30°, to be isomeric with 1 : 3-diethyl-6-methyluracil (IV; $R^1 = R^2$ = Et) but it was obviously distinct from this (Behrend and Hoffmann, *Annalen*, 1889, **253**, 71, give m. p. 52—53° for the uracil) and has been identified as (V; $R^1 = R^2$ = Et). Treatment of the

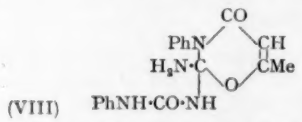


product with hot dilute acid gave ethylamine and (VI; R^1 = Et). Confirmation of these assignments was afforded by the reaction of the dihydro-2 : 4-dioxo-1 : 3-oxazine (VI; R^1 = Et) with amines—ammonia and ethylamine readily afforded the known 3-ethyl-6-methyluracil (VII; R^1 = Et, R^3 = H) and 1 : 3-diethyl-6-methyluracil (VII; $R^1 = R^3$ = Et), respectively—and by light-absorption evidence (see Table). The formation of uracils from dihydrodioxo-1 : 3-oxazines and amines affords a new and useful route to these compounds.

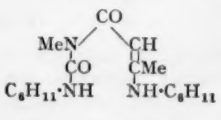
S-Methyl-, *S*-ethyl-, and *S*-benzyl-*NN'*-diphenylthiourea all reacted similarly with diketen (the last in toluene), giving the expected 1 : 3-oxazines. Acid hydrolysis of (V; $R^1 = R^2$ = Ph) gave a mixture from which only the expected dihydrodioxo-1 : 3-oxazine (VI; R^1 = Ph) was isolated. This compound with methylamine gave, 1 : 6-dimethyl-3-phenyluracil (VII; R^1 = Ph, R^3 = Me), but the reaction with ammonia was

* Part V, preceding paper. † Patents pending: B.P. Appln. 14535/52, 14644/52.

anomalous giving a product, $C_{18}H_{18}O_3N_4$, acid hydrolysis of which gave 6-methyl-3-phenyluracil, ammonia, and aniline; and, on the basis of this and light-absorption evidence (see Table), the product is regarded as (VIII), arising from two mols. of dihydrodioxo-1 : 3-oxazine and one of ammonia, with the elimination of acetoacetic acid.



(VIII)



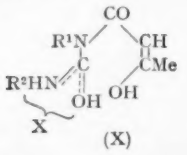
(IX)

It was not possible to replace diketen by an acetoacetic ester, which failed to react in the above preparations. Diketen was without effect on ethyl *N*-phenylurethane, which might have been expected to give the dihydrodioxo-1 : 3-oxazine (VI; R^1 = Ph) by elimination of ethanol.

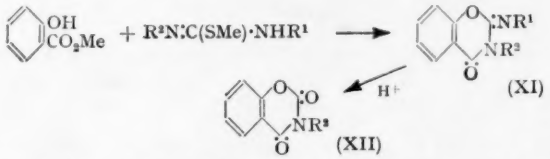
NS-Dimethyl-*N'*-phenylthiourea with diketen gave high yields of an oxazine (V; R^1 = Me, R^2 = Ph), the structure of which was established by acid hydrolysis to the dihydro-3-methyl-2 : 4-dioxo-1 : 3-oxazine (VI; R^1 = Me) and aniline. A second substance from the above hydrolysis, isomeric with the starting material, is believed to be 3 : 6-dimethyl-1-phenyluracil (IV; R^1 = Me, R^2 = Ph) which, in common with other 1-aryluracils, is not available by the usual routes. The proportions of dihydrodioxo-1 : 3-oxazine and uracil obtained were dependent on the acid concentration, lower concentrations favouring dihydrodioxo-1 : 3-oxazine formation. (VI; R^1 = Me) reacted with ammonia, methylamine, and benzylamine, giving the expected uracils (VII; R^1 = Me, R^3 = H, Me, or CH_2Ph, respectively), but with *cyclo*hexylamine two mols. of amine reacted to give a substituted β-aminocrotonamide (IX). None of the dihydrodioxo-1 : 3-oxazines condensed with aromatic amines, either alone or in the presence of catalysts.

N-Benzyl-*S*-methyl-*N'*-phenylthiourea with diketen in boiling ethylene dichloride gave a 77% yield of the oxazine (V; R^1 = CH_2Ph, R^2 = Ph); structural proof was afforded by acid hydrolysis to (VI; R^1 = CH_2Ph) and aniline, although the main product was 3-benzyl-6-methyl-1-phenyluracil (IV; R^1 = CH_2Ph, R^2 = Ph). Higher acid concentrations favoured formation of dihydrodioxo-1 : 3-oxazine, which gave the expected uracils (VII; R^1 = CH_2Ph, R^3 = H) and (VII; R^1 = CH_2Ph, R^3 = Me) with ammonia and methylamine, respectively, providing further confirmation of the structures.

Hydrolysis of the imino-oxazines (V) with aqueous alkali gave the corresponding *NN'*-disubstituted ureas, although (V; R^1 = Me, R^2 = Ph) gave also 3 : 6-dimethyl-1-phenyluracil.



(X)

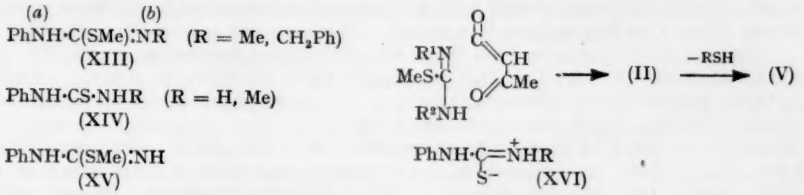


(XI) (XII)

Formation of both a dihydrodioxo-1 : 3-oxazine and a uracil by the acid hydrolysis of certain of the imino-oxazines can be ascribed to the reactions of a common intermediate (X) which, by elimination of $R^2NH_3^+$ gives the dihydrodioxo-oxazine and by removal of H_3O^+ the uracil. It is unlikely that reaction of dihydrodioxo-1 : 3-oxazines (VI) with amines proceeds through the imino-oxazines (V), since the latter do not rearrange to uracils under the weakly alkaline conditions employed. The mechanism is probably similar to that generally assigned to the formation of amides from esters with amines.

Attention is drawn to the reaction of *S*-alkylthioureas with methyl or phenyl salicylate to give benzoxazine derivatives (XI; R^1 = R^2 = Ph; R^1 = R^2 = *o*-Me·C_6H_4; R^1 = R^2 = *p*-Me·C_6H_4; R^1 = Ph, R^2 = *p*-Br·C_6H_4; R^1 = Ph, R^2 = H) (Deck and Dains, *J. Amer. Chem. Soc.*, 1933, **55**, 4986), which, on hydrolysis with acids, gave dihydrodioxobenzoxazines (XII). In the two cases in which unsymmetrical *S*-substituted thioureas were employed, the phenylimino-derivatives were obtained.

Diketen reacted with the two unsymmetrical *S*-alkylthioureas (XIII) studied to give high yields of a single product in each case. It is also significant that the acetoacetyl radical in both cases became attached to the nitrogen atom (*b*) bearing the alkyl or aralkyl substituent, giving phenylimino-derivatives. This is in contrast to the reaction with *N*-methyl-*N'*-phenylthiourea, *N*-phenylthiourea (XIV), and *S*-methylphenylthiourea (XV)



(see Part V) where, in all three cases, the acetoacetyl radical became attached to the nitrogen atom (*a*) bearing the phenyl group. It might be expected that in all cases the reagent would attack nitrogen atom (*b*) in preference to that substituted by phenyl, and, in consequence, the less basic. However, other apparent anomalies have been reported. *S*-Methylphenylthiourea on treatment with methyl iodide gives *NS*-dimethyl-*N*-phenylthiuronium iodide [*i.e.*, substitution at (*a*)](Bertram, *Ber.*, 1892, **25**, 52), whereas treatment with phenyl *iso*cyanate, which in many reactions resembles diketen in reactivity (cf. Petersen, *Ber.*, 1950, **83**, 551), gives a substituted urea arising from attack at (*b*) (Lakra and Dains, *J. Amer. Chem. Soc.*, 1929, **51**, 2224).

The reaction of diketen with substituted thioureas can possibly be explained in terms of the dipolar " zwitterion " (XVI) that has been postulated to represent most closely the structure of thioureas (cf. Taylor and Baker, " Sidwick's Organic Chemistry of Nitrogen," Oxford, 1937, p. 281), in which the more basic nitrogen atom is closely bound with the sulphur atom, leaving the less basic nitrogen atom free to react. Nevertheless, certain facts await a satisfactory explanation. It was established that the reaction of diketen with substituted *S*-alkylthioureas is not of the Diels–Alder type (as written above, the disputed acetylketen structure being assigned to diketen), since *NN*-diethyl-*S*-methyl-*N'*-phenylthiourea failed to react with diketen, showing that a replaceable hydrogen is necessary.

Light-absorption data for certain of the imino-oxazines and dioxo-1 : 3-oxazines are tabulated below. The oxazines show the absorption expected for derivatives of crotonic acid, and the values of $\lambda_{max.}$ show that the presence of the phenylimino-group causes a considerable auxochromic shift of the absorption maximum, indicating some degree of interaction between the imino-group and the conjugated system.

Light-absorption data (in ethanol solution).

	$\lambda_{max.}$, Å	$\varepsilon_{max.}$		$\lambda_{max.}$, Å	$\varepsilon_{max.}$
(V; $R^1 = R^2 = Et$)	2150 [1]	10,000	(VI; $R^1 = Et$)	2300	7,200
	2560	1,950	(VI; $R^1 = Ph$)	2340	9,550
(V; $R^1 = R^2 = Ph$)	2300	14,000			
	2500 [2]	11,000	(VIII)	2390	22,000
(V; $R^1 = Me$, $R^2 = Ph$) ...	2500	11,500		2620	10,000

[1] End absorption. [2] Inflection.

Experimental

M. p.s were determined on a Kofler block and are corrected.

3-*Ethyl*-2-*ethylimino*-2 : 3-*dihydro*-6-*methyl*-4-*oxo*-1 : 3-*oxazine* (V; $R^1 = R^2 = Et$).—*NN'*-Diethylthiourea (39·6 g.), methyl iodide (50 g.), and ethanol (200 c.c.) were refluxed for 1 hr., and most of alcohol then distilled off. The residue was treated with sodium hydroxide solution (10%; 120 c.c.) and, after being saturated with salt, the mixture was thoroughly extracted with ether to give, after drying and evaporation of the extracts, crude *NN'*-diethyl-*S*-methylthiourea (44 g.) as a pale yellow oil. This was treated in boiling benzene (50 c.c.) with diketen

(26 g.), added during 0·5 hr. with agitation; methanethiol was freely evolved. After a further 0·5 hr.'s refluxing the benzene was evaporated and the residue distilled, giving the *oxazine* (V; $R^1 = R^2 = Et$) (42·1 g., 77% yield on *NN'*-diethylthiourea), b. p. 90—93°/1 mm., m. p. 30° (Found: C, 59·7; H, 8·0; N, 15·1. $C_9H_{14}O_2N_2$ requires C, 59·3; H, 7·75; N, 15·4%). Light absorption: see Table.

3-*Ethyl*-2 : 3-*dihydro*-6-*methyl*-2 : 4-*dioxo*-1 : 3-*oxazine* (VI; $R^1 = Et$).—The oxazine (V; $R^1 = R^2 = Et$) (2·3 g.) was refluxed with a mixture of concentrated hydrochloric acid (1 c.c.) and water (10 c.c.) for 15 min., and then cooled. The separated *oxazine* (VI; $R^1 = Et$) (1·1 g.) was crystallised from light petroleum (b. p. 60—80°), giving needles, m. p. 69—70° (Found: C, 53·85; H, 5·55; N, 9·2. $C_7H_9O_3N$ requires C, 54·2; H, 5·85; N, 9·05%). Addition of alkali to the aqueous filtrate afforded ethylamine. Use of sulphuric acid in the above hydrolysis gave similar results. Light absorption: see Table.

Treatment of the 2 : 4-dioxo-1 : 3-oxazine (VI; $R^1 = Et$) (0·1 g.) with ammonia solution (*d* 0·88; 10 c.c.) gave, on evaporation, 3-ethyl-6-methyluracil, m. p. and mixed m. p. 206° (Hoebel, *Annalen*, 1907, **353**, 245, gives m. p. 195°). Similarly, treatment with 40% ethylamine gave 1 : 3-diethyl-6-methyluracil, as an oil which crystallised from ether as plates, m. p. 50—51° (Behrend and Hoffmann, *loc. cit.*, give m. p. 52—53°).

2 : 3-*Dihydro*-6-*methyl*-4-*oxo*-3-*phenyl*-2-*phenylimino*-1 : 3-*oxazine* (V; $R^1 = R^2 = Ph$).—*S*-Methyl-*NN'*-diphenylthiourea (24·2 g.) in boiling benzene (100 c.c.) was treated with diketen (8·4 g.), added with agitation during 0·5 hr. The product was refluxed for 5 hr., methanethiol being evolved, filtered and cooled, giving the *oxazine* (V; $R^1 = R^2 = Ph$) (18·9 g., 65%), which formed prisms, m. p. 184—185°, from ethyl acetate (Found: C, 73·0; H, 4·8; N, 10·2. $C_{17}H_{14}O_2N_2$ requires C, 73·35; H, 5·05; N, 10·0%). Light absorption: see Table.

S-Ethyl-*NN'*-diphenylthiourea similarly gave the corresponding oxazine in 36·5% yield. Crude *S*-benzyl-*NN'*-diphenylthiourea (cf. Werner, *J.*, 1890, 297), prepared from *NN'*-diphenylthiourea (46·0 g.) and benzyl chloride (25 g.), in toluene (100 c.c.), was treated with diketen (17·3 g.) as described above. Evaporation of the solvent left a gummy solid, which, when rubbed with benzene, gave the oxazine (20·0 g., 36%), m. p. 178—180°.

2 : 3-*Dihydro*-6-*methyl*-2 : 4-*dioxo*-3-*phenyl*-1 : 3-*oxazine* (VI; $R^1 = Ph$).—The oxazine (V; $R^1 = R^2 = Ph$) (2·0 g.) was refluxed with concentrated hydrochloric acid (1 c.c.) and water (10 c.c.) for 20 min. and then cooled. After two crystallisation of the precipitate from methanol the *oxazine* (VI; $R^1 = Ph$) was obtained as needles (0·7 g.), m. p. 170° (Found: C, 65·3; H, 4·45; N, 7·0. $C_{11}H_9O_3N$ requires C, 65·0; H, 4·45; N, 6·9%). Light absorption: see Table.

The 2 : 4-dioxo-1 : 3-oxazine (VI; $R^1 = Ph$) (0·1 g.) was warmed with aqueous methylamine (40%; 10 c.c.), and the solution then concentrated; 1 : 6-dimethyl-3-phenyluracil, m. p. and mixed m. p. 210°, was obtained (cf. Part V). Similar treatment with ammonia readily gave needles [probably (VIII)], m. p. 201°, from water (Found: C, 64·15; H, 5·4; N, 16·7. $C_{18}H_{18}O_3N_4$ requires C, 63·9; H, 5·35; N, 16·55%). Hydrolysis of (VIII) with boiling dilute hydrochloric acid gave 6-methyl-3-phenyluracil, m. p. and mixed m. p. 255—256° (Behrend, Meyer, and Buchholz, *Annalen*, 1901, **314**, 209, give m. p. 244—245°), and, on addition of alkali to the filtrate, ammonia and aniline. Light absorption of (VIII): see Table.

2 : 3-*Dihydro*-3 : 6-*dimethyl*-4-*oxo*-2-*phenylimino*-1 : 3-*oxazine* (V; $R^1 = Me$, $R^2 = Ph$).—*NS*-Dimethyl-*N'*-phenylthiourea (Deck and Dains, *loc. cit.*) (34·5 g.) in boiling benzene (50 c.c.) was treated with diketen (16·5 g.) during 0·5 hr., and refluxing continued for 3 hr., methanethiol being evolved. The solvent was evaporated and the oil (42 g.) rubbed with ether–light petroleum (b. p. 40—60°) giving the *oxazine* (V; $R^1 = Me$, $R^2 = Ph$) as a pale brown solid (30·5 g., 95%) which, on crystallisation from aqueous methanol, gave prisms, m. p. 69—70° (Found: C, 66·95; H, 5·35; N, 12·6. $C_{12}H_{12}O_2N_2$ requires C, 66·65; H, 5·6; N, 12·95%). Light absorption: see Table.

2 : 3-*Dihydro*-3 : 6-*dimethyl*-2 : 4-*dioxo*-1 : 3-*oxazine* (VI; $R^1 = Me$).—The oxazine (V; $R^1 = Me$, $R^2 = Ph$) (1·0 g.) was refluxed with concentrated hydrochloric acid (1 c.c.) and water (10 c.c.) for 20 min. On cooling, a microcrystalline powder (0·05 g.), m. p. 300—302°, was first deposited, followed by the *oxazine* (VI; $R^1 = Me$) (0·4 g.) as needles (from water), m. p. 108—109° (Found: C, 51·35; H, 4·8; N, 9·95. $C_6H_7O_3N$ requires C, 51·05; H, 5·0; N, 9·95%). Recrystallisation of the high-melting product first deposited gave 3 : 6-*dimethyl*-1-*phenyluracil* (IV; $R^1 = Me$, $R^2 = Ph$) as plates, m. p. 300—302°, from water (Found: C, 66·35; H, 5·65; N, 12·7. $C_{12}H_{12}O_2N_2$ requires C, 66·65; H, 5·6; N, 12·95%).

Further hydrolyses of the phenylimino-oxazine (V; $R^1 = Me$, $R^2 = Ph$) (10·0 g.) with the calculated amount of concentrated hydrochloric acid (4·2 c.c.) were carried out with varying amounts of water and 0·5 hr.' boiling. The solid products were isolated by means of chloroform,

and the dioxo-1 : 3-oxazine separated from the uracil by Soxhlet extraction with methanol, in which the uracil is practically insoluble. The results are presented below:

Water (c.c.)	10	20	40
Dioxo-1 : 3-oxazine (g.)	5·10	5·51	5·63
Uracil (g.)	0·80	0·49	0·28

The dioxo-1 : 3-oxazine (VI; R^1 = Me) (0·2 g.) was warmed with ammonia solution (*d* 0·88; 10 c.c.) and the solution evaporated to a small bulk, giving 3 : 6-dimethyluracil, m. p. and mixed m. p. 274° (Behrend and Hesse, *Annalen*, 1903, **329**, 348, give m. p. 261—262°). Similarly, treatment with aqueous methylamine (40%) gave 1 : 3 : 6-trimethyluracil as needles, m. p. and mixed m. p. 110° (Behrend and Hufschmidt, *Annalen*, 1905, **343**, 158, give m. p. 111—112°). The dioxo-1 : 3-oxazine (1·4 g.) and benzylamine (1·2 g.) were refluxed in ethanol (10 c.c.) for 2 hr., followed by removal of the solvent under reduced pressure and extraction of the residue with ether. Removal of the ether, trituration of the resulting oil with water and crystallisation of the solid from ether gave plates (0·85 g.), m. p. 84—85° undepressed with an authentic specimen of 1-benzyl-3 : 6-dimethyluracil (Wheeler and McFarland, *Amer. Chem. J.*, 1909, **42**, 105, give m. p. 85—86°).

When the dioxo-1 : 3-oxazine (0·1 g.) was heated with *cyclo*hexylamine (0·1 g.) at 90—100° for 1 hr. and the oil rubbed with ether, a solid (0·06 g.), m. p. 135—138°, was obtained. Crystallisation from aqueous methanol gave N-cyclo*hexyl*-N′-(β-cyclo*hexylaminocrotonyl*)-N′-*methylurea* (IX) as needles, m. p. 139—140° (Found: C, 67·55; H, 10·05; N, 12·9. $C_{18}H_{31}O_2N_3$ requires C, 67·25; H, 9·75; N, 13·1%). The material was insoluble in acid and alkali but on warming with dilute hydrochloric acid, rapid hydrolysis ensued with evolution of carbon dioxide and formation of *cyclo*hexylamine (trinitrotoluene derivative).

3-*Benzyl*-2 : 3-*dihydro*-6-*methyl*-4-*oxo*-2-*phenylimino*-1 : 3-*oxazine* (V; R^1 = CH_2Ph, R^2 = Ph).—*N*-Benzyl-*N*′-phenylthiourea (54·5 g.), methyl iodide (35 g.), and ethanol (100 c.c.) were refluxed for 1 hr., and then cooled. A solution of sodium hydroxide (9·25 g.) in water (50 c.c.) was added and solid was deposited (57 g.), m. p. 58—60°. Crystallisation from light petroleum (b. p. 60—80°) gave N-*benzyl*-S-*methyl*-N′-*phenylthiourea* as needles, m. p. 61—62° (Found: N, 10·7. $C_{15}H_{16}N_2S$ requires N, 10·9%). Diketen (17·7 g.) was added during 0·5 hr. to a solution of this thiourea (51 g.) in boiling ethylene dichloride (50 c.c.). After a further 2 hr. for refluxing, methanethiol being evolved, the solvent was removed. Crystallisation of the product from aqueous methanol gave the *oxazine* (V; R^1 = CH_2Ph, R^2 = Ph) (45 g., 77%) as needles, m. p. 77° (Found: C, 74·25; H, 5·45; N, 9·45. $C_{18}H_{16}O_2N_2$ requires C, 73·95; H, 5·5; N, 9·6%).

3-*Benzyl*-2 : 3-*dihydro*-6-*methyl*-2 : 4-*dioxo*-1 : 3-*oxazine* (VI; R^1 = CH_2Ph).—The oxazine (V; R^1 = CH_2Ph, R^2 = Ph) (5·0 g.) was refluxed with concentrated hydrochloric acid (10 c.c.) for 0·5 hr. The solid (2·7 g.) was collected and extracted with hot water, giving the 2 : 4-*dioxo*-1 : 3-*oxazine* (VI; R^1 = CH_2Ph) (1·1 g.) [prisms, m. p. 93°, from benzene–light petroleum (b. p. 40—60°)] (Found: C, 66·35; H, 5·35; N, 6·25. $C_{12}H_{11}O_3N$ requires C, 66·35; H, 5·1; N, 6·45%) and a residue of 3-*benzyl*-6-*methyl*-1-*phenyluracil* (1·4 g.) (needles, m. p. 226—227°, from ethanol) (Found: C, 74·0; H, 5·6; N, 9·35. $C_{18}H_{16}O_2N_2$ requires C, 73·95; H, 5·5; N, 9·6%). In a second experiment, the phenylimino-1 : 3-oxazine (5 g.) was refluxed with hydrochloric acid (2 c.c. of acid plus 10 c.c. of water) for 0·75 hr. Isolation as before gave the 2 : 4-dioxo-1 : 3-oxazine (0·36 g.) and the uracil (2·55 g.).

The dioxo-1 : 3-oxazine (0·1 g.) was warmed with aqueous ammonia (*d* 0·88; 5 c.c.), and the solution concentrated and allowed to crystallise, giving 3-benzyl-6-methyluracil as plates, m. p. 198° (Wheeler and McFarland, *loc. cit.*, give m. p. 194°). Similar treatment of the dioxo-1 : 3-oxazine (0·1 g.) with aqueous methylamine (30%; 3 c.c.) gave 3-benzyl-1 : 6-dimethyluracil, m. p. 166—167° (*idem*, *ibid.*, give m. p. 164°).

Alkaline Hydrolysis of Dioxo-1 : 3-*oxazines* (VI).—(*a*) The oxazine (VI; R^1 = R^2 = Ph) (1 g.) was refluxed with a mixture of sodium hydroxide solution (10%; 5 c.c.) and methanol (20 c.c.) for 2 hr. On concentration and cooling of the solution, *NN*′-diphenylurea (0·15 g.), m. p. 246°, was deposited (Young and Clark, *J.*, 1898, 367, give m. p. 238—239°).

(*b*) The oxazine (VI; R^1 = Me, R^2 = Ph) (1 g.) was hydrolysed as above giving *N*-methyl-*N*′-phenylurea (0·35 g.) as plates, m. p. 150° (Dixon, *J.*, 1895, **561**, gives m. p. 150·5—151·5°). 3 : 6-Dimethyl-1-phenyluracil (0·15 g.) (see above), m. p. 302°, was also collected from the hot hydrolysis product.

(*c*) The oxazine (VI; R^1 = CH_2Ph, R^2 = Ph) (1 g.) was hydrolysed as above, giving *N*-benzyl-*N*′-phenylurea (0·55 g.), m. p. 172° (Ley and Krafft, *Ber.*, 1907, **40**, 703, give m. p. 170°).

British Industrial Solvents, Development Dept.,
Hedon, Hull.

[*Received, August 1st*, 1953.]

*Derivatives of Acetoacetic Acid. Part VII.** α-*Acetyltetramic Acids.*†

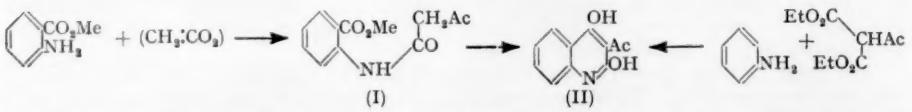
By R. N. Lacey.

[Reprint Order No. 4550.]

Methyl anthranilate was converted into the acetoacetyl derivative with diketen, and the product cyclised with sodium methoxide, giving 3-acetyl-2 : 4-dihydroxyquinoline. Esters of α-amino-acids (glycine, DL-alanine, and anilinoacetic acid) were similarly converted into the corresponding aceto-acetyl derivatives which, with sodium alkoxides, gave α-acetyltetramic acids (IV). By a similar sequence of reactions, ethyl β-aminopropionate was converted into 3-acetyl-1 : 2 : 5 : 6-tetrahydro-4-hydroxy-2-oxopyridine (V).

THE present paper is concerned with the preparation and properties of acetoacetamides from alkoxycarbonyl-amines and diketen. Methyl anthranilate reacts smoothly with diketen at 100—120°. Lyashenko and Sokolova (*J. Gen. Chem., U.S.S.R.*, 1947, **17**, 1868) found a parallel between the rate of reaction of diketen with an aromatic amine and the basic strength of the amine, and, since methyl anthranilate is a relatively weak base ($K = 1{\cdot}5 \times 10^{-12}$), the necessity for the high reaction temperature receives an explanation; aniline ($K = 5 \times 10^{-10}$) rapidly reacts with diketen at room temperature. However, the use of catalytic quantities of a *tert.*-amine led to a reduction of reaction temperature to 60—70° and a high yield of the expected acetoacetanilide (cf. Perekalin and Lerner, *J. Gen. Chem., U.S.S.R.*, 1951, **21**, 1995; Lacey and Connolly, B.P. Appln. 20198/1951). The success achieved is in contrast with the failure of diketen to react with methyl salicylate (Part IV).

It was shown in Part IV that the acetoacetates of α-hydroxy-carboxylates were readily cyclised to α-acetyltetronic acids by means of sodium or, in certain cases better, by alcoholic sodium alkoxide. Treatment of methyl *o*-acetoacetamidobenzoate (I) with sodium in toluene caused some conversion into 3-acetyl-2 : 4-dihydroxyquinoline (II) but better results were obtained by using sodium methoxide in methanol. Compounds similar to (II) had been prepared by Vaughan (*J. Amer. Chem. Soc.*, 1946, **68**, 324) by the condensation of *p*-methoxy- or *m*-chloro-aniline with acetylmalonic ester in refluxing nitrobenzene solution. Since (II) itself had not been prepared by Vaughan, aniline was condensed with acetyl-malonic ester, giving a product identical with that obtained by the above cyclisation. The quinoline (II) was remarkable in that, on treatment with phenylhydrazine in acetic acid solution, acetylation, presumably of the 4-hydroxyl, accompanied phenylhydrazone formation.



(I) (II)

Ethyl α-aminoacetate was liberated from its hydrochloride by treatment with alcoholic sodium ethoxide; the solution so obtained reacted rapidly with diketen at a low temperature, giving the expected acetoacetamide (III; R = R′ = H). When this was refluxed with sodium methoxide in methanol–benzene, self-condensation gave α-acetyl-tetramic acid (IV; R = R′ = H). The product liberated carbon dioxide from sodium hydrogen carbonate and gave a red colour with ferric chloride in close parallel with the strongly acidic properties of α-acetyltetronic acids (see Part IV).

Anschütz and Böcker (*Annalen*, 1909, **368**, 53) claimed to have prepared α-ethoxy-carbonyl-γ-phenyltetramic acid, but, since the substance did not possess acidic properties, it does not appear to be well characterised. Further references to pyrrolidine-2 : 4-diones include Benary (*Ber.*, 1911, **44**, 1763), Hoffmann-La Roche (G.P. 695,330), and three recent papers kindly pointed out by a referee (Cornforth and Huang, *J.*, 1948, 1958; King

* Part VI, preceding paper. † Patent pending: B.P. Appln. 2260/1951.

and McMillan, *J. Amer. Chem. Soc.*, 1950, **72**, 1236; and Larsen and Bernstein *ibid.*, p. 4447).

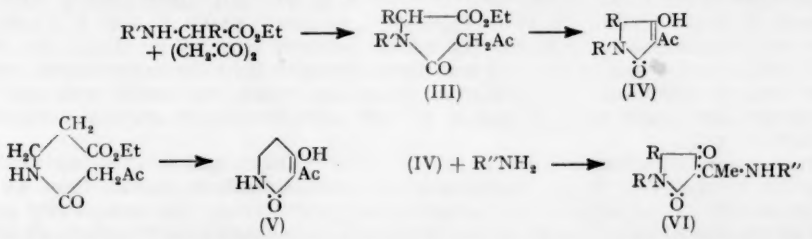
Similarly, DL-α-alanine ethyl ester was liberated from its hydrochloride as above or by Hillman's method (*Z. Naturforsch.*, 1946, **1**, 682) and treated with diketen in the cold. The acetoacetamide (III; R = Me, R′ = H) was obtained as an oil which decomposed when heated, but treatment of the crude product with sodium ethoxide in ethanol–benzene gave α-acetyl-γ-methyltetramic acid (IV; R = Me, R′ = H). Ethyl anilinoacetate was converted into (III; R = H, R′ = Ph) by reaction with diketen in boiling benzene. The reaction was slower than with the two amino-esters previously studied, the phenyl group greatly reducing the basicity of the amino-group. Cyclisation of the acetoacetamide with sodium ethoxide in ethanol–benzene gave the tetramic acid (IV; R = H, R′ = Ph) in 85% overall yield.

Attempts to effect the self-condensation of the acetoacetate of ethyl β-hydroxybutyrate (Part IV) were unsuccessful, but, by the above methods β-alanine ethyl ester was converted into the acetoacetamide, which, on treatment with sodium ethoxide in ethanol–toluene followed by prolonged refluxing, gave a small yield of 3-acetyl-1 : 2 : 5 : 6-tetrahydro-4-hydroxy-2-oxopyridine (V), which was not rigorously characterised although it was shown to be soluble in sodium hydrogen carbonate solution, insoluble in dilute mineral acid, to give the expected red colour with ferric chloride, and to exhibit light-absorption properties closely similar to those of the α-acetyltetramic acids described above (see Table).

Light-absorption data (in ethanol solution).

	$\lambda_{max.}$, Å	$\varepsilon_{max.}$	$\lambda_{max.}$, Å	$\varepsilon_{max.}$
(IV; R = R′ = H)	2390	9,550	2770	13,500
(IV; R = Me, R′ = H)	2400	5,250	2800	10,850
(IV; R = H, R′ = Ph)	2580	14,500	2820	26,050
(V)	2300 (infl.)	6,300	2750	15,000
(VI; R = Me, R′ = H, R″ = Ph)	2650	15,900	3300	27,600
(VI; R = H, R′ = R″ = Ph)	2650	16,000	3300	27,600
(VI; R = H, R′ = Ph, R″ = CH_2Ph)	2660	17,800	3200	26,300

α-Acetyltetramic acids reacted with primary amines, giving the "amides" which possess the α-enamine structure (VI) found in the "amides" of α-acetyltetronic acids (cf. Part IV), as shown by the light-absorption properties (see Table). The acids were resistant to alkaline hydrolysis and both α-acetyl-γ-methyltetramic acid and α-acetyl-*N*-phenyltetramic acid were substantially unchanged after several hours' boiling with 10% sodium hydroxide. Clutterbuck, Raistrick, and Reuter (*Biochem. J.*, 1935, **29**, 300) showed that α-acetyltetronic acids may be hydrogenated to α-ethyltetronic acids over a



palladium on charcoal catalyst. However (IV; R = Me, R′ = H) and (IV; R = H, R′ = Ph) resisted hydrogenation under these conditions which, in confirmation of the work of Clutterbuck *et al.* (*loc. cit.*), were found adequate for the reduction of α-acetyltetronic acids. The bromination of α-acetyltetramic acids did not proceed analogously to that of α-acetyltetronic acids (Clutterbuck *et al.*, *loc. cit.*) (cf. Part IV), but gave only intractable products.

The absorption spectra of the α-acetyltetramic acids (see Table) were closely similar to those recorded for α-acetyltetronic acids (cf. Part IV). Two bands were exhibited, ascribed to (*a*) the αβ-unsaturated carboxyl group ($\lambda_{max.}$ 2300—2600 Å) and (*b*) the system

C(OH):CAc ($\lambda_{max.}$ 2650—2850 Å). Comparison of these values with those for α-acetyltetronic acids showed that both bands were shifted to higher wave-lengths ($\Delta\lambda \sim 100$—150 Å) by the replacement of the ester O of the α-acetyltetronic acids by NH, and replacement of O by NPh caused a larger shift (280 Å) in band (*a*), as would be expected, with only a small shift in band (*b*) over that obtained by replacement with NH. The facts support the above explanation of the form of the absorption curves, although the shift in band (*b*) would indicate that the band is not attributable to the C(OH):CAc system in isolation, for the introduction of NH would be expected, on the basis of the above simple reasoning, to affect only band (*a*). The " amides " of α-acetyltetramic acids (VI) also exhibit two absorption bands as did the " amides " of α-acetyltetronic acids (cf. Part IV). Very large auxochromic shifts of the absorption maxima ($\Delta\lambda \sim 300$—400 Å) were observed between the " amides " of tetronic acids and those of tetramic acids.

Attempts to prepare the sulphur analogue of α-acetyltetronic acid by the reaction of diketen with methyl thioglycollate followed by treatment with sodium in toluene were unsuccessful, giving only dehydroacetic acid.

Experimental

M. p.s were determined on a Kofler block and are corrected.

Methyl o-Acetoacetamidobenzoate (I).—(*a*) Diketen (21 g.) was added to methyl anthranilate (38 g.) with stirring during 20 min. The product was then heated at 110—120° for 0·5 hr., cooled, and triturated with light petroleum, giving a solid (51·5 g., 86·5%), m. p. 71·5—73°. Crystallisation from benzene–light petroleum (b. p. 60—80°) gave the *amide* (I) as prisms, m. p. 79—80° (Found: C, 61·1; H, 5·65. $C_{12}H_{13}O_4N$ requires C, 61·25; H, 5·55%).

(*b*) To an agitated solution of methyl anthranilate (76 g.) in benzene (100 c.c.) containing triethylamine (1 c.c.) at 60—70° diketen (43 g.) was added during 0·75 hr. After a further 0·5 hr. at 70° removal of solvent gave the amide (104 g., 88·5%), m. p. 74°.

3-Acetyl-2 : 4-dihydroxyquinoline (II).—(*a*) The amide (I) (59 g.) in toluene (100 c.c.) was added to a suspension of finely-divided sodium (6 g.) in toluene (100 c.c.), and the mixture heated with stirring for 3 hr., and then set aside overnight. The mixture was acidified with dilute sulphuric acid, and the product (7·2 g.) crystallised from acetic acid giving the *quinoline* (II), m. p. 259° (Found: C, 64·8; H, 4·7. $C_{11}H_9O_3N$ requires C, 65·0; H, 4·45%). From the solvent layer after acidification starting material (19·8 g.) was obtained.

(*b*) A solution of sodium methoxide (from 6 g. of sodium in 100 c.c. of methanol) was added to an agitated solution of the above amide (59 g.) in ether (100 c.c.) and methanol (50 c.c.) during 0·5 hr. After being refluxed overnight, the mixture was acidified as before, giving the above quinoline (48·6 g., 96%), m. p. 255°. Refluxing of a mixture of the quinoline (II) (1 g.) and phenylhydrazine (2 g.) in acetic acid (10 c.c.) for 0·5 hr., followed by the addition of water, gave the *phenylhydrazone acetate*, as red micro-crystals, m. p. 206—207° (from aqueous methanol) (Found: C, 68·55; H, 5·35; N, 12·5. $C_{19}H_{17}O_3N_3$ requires C, 68·05; H, 5·1; N, 12·55%).

(*c*) (cf. Vaughan, *loc. cit.*) Aniline (4·5 g.), acetomalonic ester (20 g.; Lund, *Ber.*, 1934, **67**, *B*, 935), and nitrobenzene (150 c.c.) were heated beneath a short distillation column, ethanol being removed as formed. The precipitate formed on cooling was washed with ether and crystallised from acetic acid; it had m. p. 259° undepressed with material obtained by methods (*a*) or (*b*).

Ethyl Acetoacetamidoacetate (III; R = R′ = H).—Ethyl aminoacetate hydrochloride (42 g.), in warm ethanol (80 c.c.), was treated with ethanolic sodium ethoxide (from 6·9 g. of sodium and 80 c.c. of ethanol) with agitation and rapid cooling. The precipitated sodium chloride was filtered off and the alcoholic ethyl aminoacetate thus obtained treated with diketen (26 g.) added during 20 min. at <5°. After 1 hr. at room temperature, the solvent was removed at reduced pressure, and the residue extracted with ether, leaving a small amount of sodium chloride. Evaporation of the ether gave the *amide* (49 g., 87%), m. p. 45°, readily soluble in ethanol, water and ether, but insoluble in light petroleum. Crystallisation from ether gave needles, m. p. 49—50° (Found: C, 51·1; H, 6·95; N, 7·3. $C_8H_{13}O_4N$ requires C, 51·35; H, 7·0; N, 7·5%).

α-Acetyltetramic Acid (IV; R = R′ = H).—Ethyl acetoacetamidoacetate (49 g.) in benzene (100 c.c.) was refluxed with agitation with a solution of sodium methoxide (from 7 g. of sodium and 80 c.c. of methanol) for 3 hr. and set aside overnight. Water (100 c.c.) was added and the solvent layer extracted with water (2 × 50 c.c.). The aqueous extracts were carefully acidified

with concentrated sulphuric acid (16 g.) and repeatedly extracted with ether, giving, after washing, drying, and evaporation, *α-acetyltetramic acid* (IV; R = R′ = H) (crude yield: 28·2 g., 76%) which formed micro-crystals, m. p. 155°, from ethyl acetate (Found: C, 51·4; H, 5·1; N, 10·2. $C_6H_7O_3N$ requires C, 51·05; H, 5·0; N, 9·95%). Light absorption: see Table.

The 2 : 4-*dinitrophenylhydrazone* crystallised from aqueous acetic acid as dark red prisms, m. p. 229° (decomp.) (Found: C, 45·1; H, 3·7; N, 21·4. $C_{12}H_{11}O_6N_5$ requires C, 44·85; H, 3·45; N, 21·8%). The *phenylhydrazone* formed golden needles, m. p. 191—192°, from aqueous methanol (Found: C, 62·55; H, 5·6; N, 17·8. $C_{12}H_{13}O_2N_3$ requires C, 62·3; H, 5·65; N, 18·15%).

Ethyl α-Acetoacetamidopropionate (III; R = Me, R′ = H).—(*a*) Ethyl DL-α-aminopropionate hydrochloride (25 g.) in warm ethanol (50 c.c.) was treated with a solution of sodium ethoxide (from 3·7 g. of sodium and 50 c.c. of ethanol). The product was rapidly cooled, filtered, and treated with diketen (14·5 g.), added to the agitated solution during 1 hr. at <10°. After 1 hr. at room temperature, the product was evaporated at reduced pressure, giving a pale yellow oil (28 g., 85·5%).

(*b*) Ethyl DL-α-aminopropionate hydrochloride (20 g.) was stirred at room temperature with a solution of ammonia (2·4 g.) in chloroform (90 c.c.) for 3 hr. The ammonium chloride was filtered off and the solution concentrated somewhat in a stream of air at reduced pressure to remove the excess of ammonia. Diketen (11·5 g.) was added to the agitated solution at room temperature during 0·5 hr. and, after a further 0·5 hr., the solvent was removed, giving the amide (24 g., 91·5%), which decomposed on attempted distillation at 12 mm.

α-Acetyl-γ-methyltetramic Acid (IV; R = Me, R′ = H).—The above crude amide (28 g.), benzene, and alcoholic sodium ethoxide (from 3·75 g. of sodium and 50 c.c. of ethanol) were refluxed with agitation and then set aside overnight. Water (150 c.c.) was added to dissolve the sodium salts, and the benzene layer was extracted with water (2 × 25 c.c.). The combined extracts were carefully neutralised (concentrated sulphuric acid) and concentrated *in vacuo* at 20—25° (to about 100 c.c.), some solid separating. Thorough extraction with ether gave, on removal of solvent, the *tetramic acid* (11·5 g., 53·5%), which crystallised from ethyl acetate–light petroleum (b. p. 60—80°) as needles, m. p. 115—116° (Found: C, 54·0; H, 5·55; N, 9·2. $C_7H_9O_3N$ requires C, 54·2; H, 5·85; N, 9·05%). The 2 : 4-*dinitrophenylhydrazone* crystallised from aqueous acetic acid as red microcrystals, m. p. 223° (decomp.) (Found: N, 21·2. $C_{13}H_{13}O_6N_5$ requires N, 20·9%).

α-Acetyl-γ-methyltetramic acid (1 g.) and aniline (1 g.) were refluxed in ethanol for 30 min., and water then added, giving the *anilide* (VI; R = Me, R′ = H, R″ = Ph) (crude yield: 1·3 g.), needles, m. p. 165°, from aqueous ethanol (Found: C, 67·7; H, 6·25; N, 12·1. $C_{13}H_{14}O_2N_2$ requires C, 67·8; H, 6·15; N, 12·15%).

α-Acetyl-N-phenyltetramic Acid (IV; R = H, R′ = Ph).—Ethyl anilinoacetate (33·4 g.; cf. Gault, *Bull. Soc. chim.*, 1908, **3**, 370) in boiling benzene (50 c.c.) was treated during 0·5 hr. with diketen (17·6 g.), refluxing continued for a further 1·5 hr., and the solvent then removed. To a solution of the resulting oil (51 g.) in benzene (100 c.c.) was added alcoholic sodium ethoxide (from 5 g. of sodium in 50 c.c. of ethanol). The mixture was refluxed with agitation for 5 hr. and then set aside overnight. The sodium salts were extracted with water and the aqueous extract shaken with ether. Acidification with dilute sulphuric acid and crystallisation of the precipitate from ethanol gave the *tetramic acid* (37 g., 85% overall), m. p. 145°. Crystallisation from ethyl acetate gave pale brown plates, m. p. 148° (Found: C, 66·6; H, 5·25; N, 6·5. $C_{12}H_{11}O_3N$ requires C, 66·35; H, 5·1; N, 6·45%).

The 2 : 4-*dinitrophenylhydrazone* was prepared in ethanol and formed a red precipitate, m. p. 263° (decomp.), practically insoluble in most solvents (Found: C, 54·5; H, 3·9; N, 17·0. $C_{18}H_{15}O_6N_5$ requires C, 54·4; H, 3·8; N, 17·65%). The *phenylhydrazone* crystallised as pale brown plates, m. p. 198—199°, from aqueous acetic acid (Found: C, 70·35; H, 5·9; N, 13·7. $C_{18}H_{17}O_2N_3$ requires C, 70·35; H, 5·6; N, 13·7%).

α-Acetyl-*N*-phenyltetramic acid (1 g.), aniline (0·5 g.), and ethanol (10 c.c.) were refluxed for 5 min. Water was added, giving the *anilide* (VI; R = H, R′ = R″ = Ph) (1·1 g.), which crystallised from aqueous ethanol as needles, m. p. 142—143° (Found: C, 73·85; H, 5·5; N, 9·5. $C_{18}H_{16}O_2N_2$ requires C, 73·95; H, 5·45; N, 9·6%). Light absorption: see Table.

The tetramic acid (1 g.), benzylamine (1 g.), water (2 c.c.), and methanol (5 c.c.) were refluxed for 10 min. and allowed to cool. The *benzylamide* (VI; R = H, R′ = Ph, R″ = CH_2Ph) crystallised from aqueous methanol as needles, m. p. 114—115° (Found: C, 74·4; H, 6·05; N, 9·1. $C_{19}H_{18}O_2N_2$ requires C, 74·45; H, 5·95; N, 9·15%). Light absorption: see Table.

3-Acetyl-1 : 2 : 5 : 6-tetrahydro-4-hydroxy-2-oxopyridine (V).—A solution of β-alanine ethyl ester hydrochloride (46 g.) in ethanol (50 c.c.) was treated with sodium ethoxide (from 6·9 g. of sodium and 80 c.c. of ethanol), and the product was cooled and filtered. Diketen (26 g.) was added with agitation at 5—10° during 0·5 hr. after which the mixture was stirred at 20° for a further 0·5 hr. Evaporation of the solvent afforded the acetoacetamide as a pale yellow oil (44 g.) which was used directly for the next stage.

The crude acetoacetamide (42 g.) in toluene (100 c.c.) and a solution of sodium ethoxide (from 7 g. of sodium and 80 c.c. of ethanol) was refluxed for 20 hr. The product was acidified with dilute hydrochloric acid and thoroughly extracted with ether, giving an oil (4·1 g.) from which, on being rubbed with methanol, the *pyridone* (1·3 g.) separated; this formed needles, m. p. 192°, from methanol (Found: C, 54·1; H, 6·05; N, 8·85. $C_7H_9O_3N$ requires C, 54·2; H, 5·85; N, 9·05%). Light absorption: see Table.

BRITISH INDUSTRIAL SOLVENTS, DEVELOPMENT DEPT.,
HEDON, HULL.

[*Received, August 1st*, 1953.]

Derivatives of Acetoacetic Acid. Part VIII. The Synthesis of Coumarins from Aryl Acetoacetates.†*

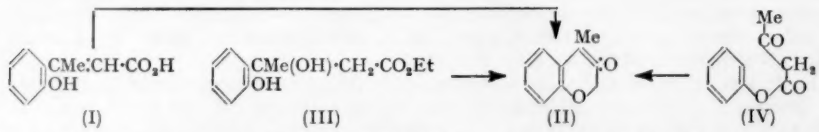
By R. N. LACEY.

[Reprint Order No. 4551.]

Aryl acetoacetates, which are readily obtained by reaction of a phenol with diketen in the presence of a basic catalyst, *e.g.*, triethylamine, are converted into coumarins by sulphuric acid. The yields obtained from the acetoacetates of a variety of substituted phenols, in general, ran parallel to those obtained from the Pechmann reaction.

Since aryl acetoacetates did not give chromones with phosphoric oxide, the mechanism postulated by Ahmed and Desai (*Proc. Indian Acad. Sci.*, 1937, **5**, *A*, 277) for the Simonis reaction must be rejected. It was established that aryl acetoacetates under these conditions were converted, in low yield, into aryl 2 : 6-dimethyl-4-pyrone-3-carboxylates.

Two essentially similar views have been put forward regarding the mechanism of the Pechmann synthesis of coumarins from phenols and β-keto-esters (cf. Sethna and Shah, *Chem. Reviews*, 1945, **36**, 1; Wawzonek, "Heterocyclic Compounds," Edited by Elderfield, Wiley, 1951, Vol. II, p. 181). Robertson, Waters, and Jones (*J.*, 1932, 1681) suggested that a substituted cinnamic acid (I) is an intermediate, whilst Ahmed and Desai (*Proc. Indian Acad. Sci.*, 1937, **5**, *A*, 277) believed that the intermediate is a β-hydroxy-β-phenylbutyric ester (III). A third proposal, that of Dallemagne and Martinet (*Bull. Soc. chim.*, 1950, **17**, 1132), will be discussed later.



These views do not preclude the possibility that the reaction proceeds through a phenyl acetoacetate (IV) which may cyclise if an activated hydrogen atom is present in the *ortho*-position. Hofheim and Schmidt (U.S.P. 2,351,366) claimed the preparation of phenyl acetoacetate from diketen and phenol in the presence of basic catalysts, and we have found this method to be a general one. Aryl acetoacetates were generally unstable, solid esters often liquefying with formation of the parent phenol within a few weeks. Liquid esters decomposed on attempted distillation.

Aryl acetoacetates, in many cases, cyclised on treatment with sulphuric acid: the

* Part VII, preceding paper.
† B.P. 682,457 (2/2/1950), see also Nordt and Delfs, G.P. 823,140 (3/12/1949).

results are tabulated below together with the yields afforded by the Pechmann reaction as described in the literature.

The results show that the yields of coumarins obtained from aryl acetoacetates are, in most cases, similar to those obtained in the Pechmann reaction, and that the effect of electron-donating substituents is similar in both reactions (cf. Pechmann and Duisberg, *loc. cit.*; Fries and Klostermann, *loc. cit.*; Clayton, *loc. cit.*). The yields obtained from the tolyl and xylyl esters indicate that the effects of directive substituents on coumarin yield are in the order ***para*** > ***meta*** > ***ortho*** ~ ***vic.-meta*** to the point of attack in the cyclisation reaction, ***ortho*** and ***vic.-meta*** (***i.e.***, adjacent to the ester group) substituents being without significant directive influence.

Dey and Lakshminarayanan (*J. Indian Chem. Soc.*, 1932, **9**, 153) found that the Pechmann condensation of β-naphthol with acetoacetic ester gave both a benzocoumarin and a benzochromone. β-Naphthyl acetoacetate with 90% sulphuric acid gave a poor yield of a mixture from which was obtained the expected styryl derivative of 2-methyl-5 : 6-benzochromone, indicating that the product was probably similar to that obtained in the Pechmann reaction.

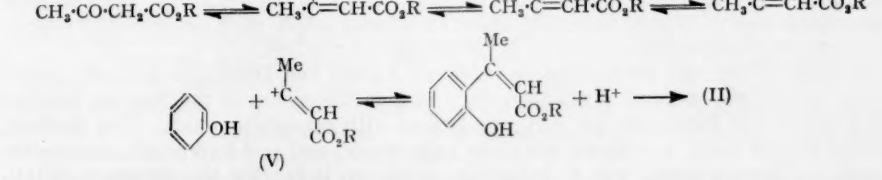
	H_2SO_4, %	Coumarin, %	Lit. yield, %
Phenol	75	11	21 [1]
		14 [2]	30—40 [2]
Resorcinol	98	85	82—90 [3]
		95·5 [4]	
Quinol	75	36·5	20—34 [5]
Catechol	75—98	nil	nil [6]
Pyrogallol	98	69	— [7]
m-Cresol	75	75	71 [8]
p- ,, ...	,,	71	40 [8]
			70 [9]
o- ,, ...	,,	19	— [10]
2 : 3-Xylenol * ...	75	63·5	—
2 : 4- ,, * ...	90	48	50 [11]
			97 [12]
2 : 5- ,, * ...	75—98	nil	nil [13]
3 : 4- ,, * ...	75	87	58 [11]
3 : 5- ,, * ...	90	49·5	30—40 [11, 14]
α-Naphthol	80	100	85—100 [15]
p-Chlorophenol	75	1·75	3 [14]
4-Chloro-*m*-cresol	,,	1·1	— [16]

* OH = 1.

[1] Peters and Simonis, *Ber.*, 1908, **41**, 831. [2] Sethna, Shah, and Shah, *Current Sci.*, 1937, **6**, 93 ($AlCl_3$ was used as condensing agent). [3] *Organic Syntheses*, Wiley, 1941, Vol. **21**, 23. [4] Figures refer to use of hydrochloric acid in acetic acid as condensing agent. [5] Borsche, *Ber.*, 1907, **40**, 2732; de Benneville and Connor, *J. Amer. Chem. Soc.*, 1940, **62**, 3067. [6] Pechmann and Graeger, *Ber.*, 1901, **34**, 378. [7] Pechmann and Duisberg, *Ber.*, 1883, **16**, 2119, yield not given. [8] Fries and Klostermann, *Ber.*, 1906, **39**, 871. [9] Patel and Bokil, *Chem. Abs.*, 1943, **37**, 5969 (80% sulphuric acid being used). [10] The condensation with sulphuric acid fails in this case although the use of aluminium trichloride affords the coumarin (ref. 2 above). [11] Clayton, *J.*, 1908, 2016. [12] Flynn and Robertson, *J.*, 1936, 215 (86% sulphuric acid being used). [13] Goodall and Robertson, *ibid.*, p. 426. [14] Adams and Mecorney, *J. Amer. Chem. Soc.*, 1944, **66**, 802. [15] Robertson, Sandrock, and Hendry, *J.*, 1931, 2426; Auwers and Meissner, *Annalen*, 1924, **439**, 132. [16] Chakravarti and Bannerjee, *J. Ind. Chem. Soc.*, 1936, **13**, 619; yield not given.

Adams and Mecorney (*loc. cit.*) showed 4-chloro-3 : 5-xylenol to be unique in giving only a chromone on condensation with acetoacetic ester and sulphuric acid. 4-Chloro-3 : 5-xylyl acetoacetate was readily hydrolysed by 75% sulphuric acid but 98% acid gave a 33% yield of 6-chloro-2 : 5 : 7-trimethylchromone.

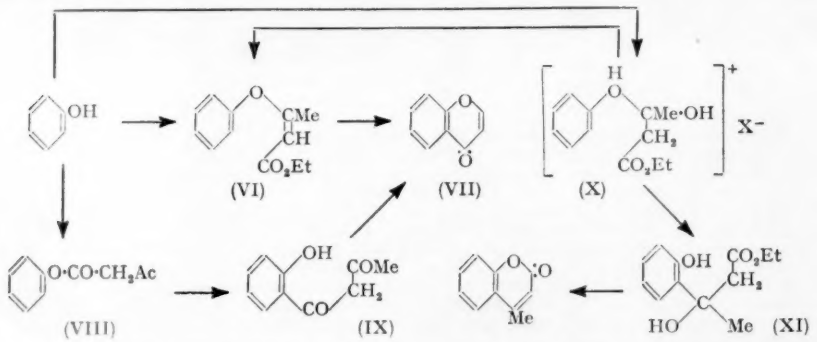
The results obtained are not contrary to the mechanism suggested by Robertson, Waters, and Jones (*loc. cit.*), although the possibility that the Pechmann condensation may



proceed *via* the aryl acetoacetate has been demonstrated. In either case, the controlling step is the condensation of the ester on the *ortho*-position of the phenol, and it is suggested that, for the Pechmann reaction, this involves first the formation of the carbonium ion (V)

which may then attack the nucleus in the manner usual in aromatic cationoid reactions. Such alkylations are reversible and the condensation would proceed only if substitution takes place in the *ortho* position so that coumarin formation follows (a π-complex between the carbonium ion and the aromatic system might afford a more accurate description of the transition state). Accepted theories concerning the orientation of cationoid substitution explain many of the results obtained by using substituted phenols, although the question is complicated by such side-reactions as sulphonation and hydrolysis.

The Simonis reaction between phenols and β-keto-esters, giving chromones (Petschek and Simonis, *Ber.*, 1913, **46**, 2014), takes place only in the presence of phosphoric oxide, phosphorus oxychloride, or, in very exceptional cases, with sulphuric acid. Three mechanisms have been proposed: the first involving the formation of a β-phenoxyacrylic acid derivative (VI) followed by ring closure to the chromone (VII) (Robertson, Waters, and Jones, *loc. cit.*), and the second proceeding *via* a phenyl acetoacetate (VIII) followed by a Fries type of rearrangement to an *o*-acetoacetylphenol (IX) and subsequent ring closure (Ahmed and Desai, *loc. cit.*). In the third mechanism (Dallemagne and Martinet, *loc. cit.*) it is supposed that both the Pechmann and the Simonis reaction proceed through the 'onium salt (X) formed by combination of the phenol, β-ketonic ester, and the acid catalyst. This hypothetical intermediate, according to the French workers, can either dehydrate to a β-phenoxyacrylic ester and thence to a chromone (favoured by α-substitution of the keto-ester and by increased acidity of the phenol, *e.g.*, with halogen or nitro-substitution), or the intermediate may rearrange to (XI), which on elimination of water and alcohol would afford the coumarin.

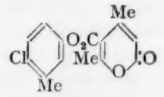
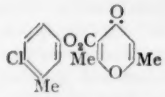


There seems little essential difference between this mechanism for chromone formation and that of Roberston *et al.* (*loc. cit.*). Since many coumarins are formed in very high yield, and in many cases even under the conditions of the Simonis reaction, which, even in favourable cases, gives chromones only in poor yields, it is necessary to assume that, in Dallemagne and Martinet's mechanism, the rearrangement to (XI) must take place much more readily than does the relatively simple dehydration to (VI). Also, the proposed mechanism does not account for recent observations by Mentzer and his co-workers (Mentzer, Molho, and Vercier, *Compt. rend.*, 1952, **232**, 1488; Mentzer and Pillon, *ibid.*, 1952, **234**, 444) that certain substituted phenols, which in the Pechmann reaction give coumarins in high yield (*e.g.*, resorcinol), afford chromones simply when heated with a β-keto-ester, *e.g.*, ethyl α-benzylacetoacetate, in the absence of catalyst.

In order to test the mechanism proposed by Ahmed and Desai (*loc. cit.*), the aceto-acetate of 4-chloro-*m*-cresol, a phenol known to give chromones in the Simonis reaction (Chakravarti and Bannerjee, *loc. cit.*), was heated with phosphoric oxide. The product, isolated in poor yield, was shown not to be a chromone, and acid hydrolysis gave carbon dioxide, 4-chloro-*m*-cresol, and 2 : 6-dimethyl-γ-pyrone, indicating the structure (XIII). The possible formulation (XII) was eliminated by an independent synthesis of this substance. The absence of chromone disproves Ahmed and Desai's mechanism.

It was also shown that the conversion of an aryl acetoacetate into an aryl 2 : 6-

dimethyl-γ-pyrone-3-carboxylate by phosphoric oxide is a general reaction, exhibited by phenols (*a*) which readily afford coumarins in the Pechmann reaction, *e.g.*, 3 : 4-xylenol, (*b*) which fail to give coumarins but give chromones in the Simonis reaction, *e.g.*, 2 : 5-xylenol, and (*c*) which give coumarins and chromones in the Pechmann and Simonis reactions, respectively, *e.g.*, 2 : 4-xylenol and 4-chloro-*m*-cresol.

(XII)   (XIII)

A most interesting parallel may be drawn between the above reaction and the Simonis reaction on the one hand, both taking place in the presence of phosphoric oxide to give derivatives of γ-pyrone, and, on the other hand, the formation of *iso*dehydroacetic acid (and ester) from the self-condensation of acetoacetic ester and the Pechmann reaction, both being effected by sulphuric acid, giving derivatives of α-pyrone. The action of phosphoric oxide in the Simonis reaction and in the formation of phenyl 2 : 6-dimethyl-γ-pyrone-3-carboxylates, is that of a dehydration catalyst causing the linkage, with elimination of water, of an enol and a phenol group and of two enol groups, respectively. The uncatalysed formation of chromones observed by Mentzer *et al.* (*loc. cit.*) can possibly be attributed to high-temperature etherification to the phenoxyacrylic ester, followed by cyclisation.

Experimental

M. p.s were carried out using a Kofler block and are corrected.

Phenyl Acetoacetate.—Diketen (84 g.) was added dropwise during 1 hr. to an agitated mixture of phenol (94 g.) and triethylamine (0·5 c.c.) at 70—80°. After a further 0·5 hr.' heating, an almost quantitative yield was obtained of *phenyl acetoacetate*; this formed prisms, m. p. 48—49°, from chloroform–light petroleum (b. p. 60—80°) (Found: C, 67·55; H, 5·65. $C_{10}H_{10}O_3$ requires C, 67·4; H, 5·6%). Phenyl acetoacetate decomposed to phenol on attempted distillation at 1 mm.; it is believed that the product, b. p. 130—142°/17 mm., obtained by Hofheim and Schmidt (*loc. cit.*) must have been a mixture.

This ester (10 g.) and sulphuric acid (75%; 30 c.c.) were heated at 50° for 6 hr., and then poured into water. An ethereal extract after treatment with sodium hydroxide solution to remove phenol, and evaporation, gave 4-methylcoumarin (1·0 g., 11%), m. p. 88° (Peters and Simonis, *loc. cit.*, give m. p. 90°).

To a solution of phenyl acetoacetate (89 g.) in nitrobenzene (100 c.c.) at 100° was added anhydrous aluminium trichloride (67 g.) in nitrobenzene (300 c.c.) with agitation during 0·5 hr. After 3 hr. at 100°, the product was cooled and shaken with hydrochloric acid (50 c.c. of concentrated acid and 50 c.c. of water); the oily layer was distilled, giving 4-methylcoumarin (11·0 g., 14%), b. p. 180°/15 mm.

m-*Hydroxyphenyl Acetoacetate.*—An agitated suspension of resorcinol (55 g.) in boiling benzene (200 c.c.) containing triethylamine (0·4 c.c.) was treated with diketen (45 g.) added during 1 hr., and heating was continued for a further 0·5 hr. The solvents were then removed under reduced pressure, giving the *ester* (96 g., 99%), which, on crystallisation from aqueous methanol, formed plates, m. p. 103° (Found: C, 61·9; H, 5·2. $C_{10}H_{10}O_4$ requires C, 61·85; H, 5·2%).

The acetoacetate (48·5 g.) was added during 15 min. to sulphuric acid (98%; 100 c.c.) with agitation and cooling, the temperature being maintained at 70°. After being heated at 70° for a further 0·5 hr. the deep red solution was poured into water, giving 7-hydroxy-4-methylcoumarin (37·4 g., 85%), which formed needles, m. p. 186°, from methanol (Pechmann and Duisberg, *loc. cit.*, give m. p. 185°). A solution of the ester (19·4 g.) in acetic acid (50 c.c.) was saturated with dry hydrogen chloride. Next morning the product was poured into water, giving the coumarin (16·8 g., 95·5%), m. p. 180—182°.

p-*Hydroxyphenyl Acetoacetate.*—This *acetoacetate* was prepared in 98% yield (crude) from quinol, as described for the *meta*-compound, and formed prisms, m. p. 98°, from ethyl acetate–light petroleum (b. p. 60—80°) (Found: C, 61·7; H, 5·3%).

The ester (10 g.) was heated with sulphuric acid (75—80%) at 50° for 24 hr. and then poured

into water. 6-Hydroxy-4-methylcoumarin had m. p. 248° after crystallisation from aqueous ethanol (Borsche, *loc. cit.*, gives m. p. 243°).

o-*Hydroxyphenyl Acetoacetate.*—This ester was obtained from catechol as an oil which failed to give any coumarin on treatment with 75—98% sulphuric acid.

Pyrogallol Monoacetoacetate.—The reaction of pyrogallol with diketen as previously described, followed by the removal of solvent, gave an oil which, although it slowly solidified, could not be purified by recrystallisation. The crude product (20 g.) and concentrated sulphuric acid (30 c.c.) were kept at 60—70° for 0·5 hr., and then poured into water. The precipitate (12·5 g., 69%), on crystallisation from aqueous methanol, gave 7 : 8-dihydroxy-4-methylcoumarin, m. p. 244° (Pechmann and Duisberg, *loc. cit.*, give m. p. 235°).

m-*Tolyl Acetoacetate.*—The ester was prepared from *m*-cresol (54 g.), triethylamine (0·5 c.c.) and diketen (42 g.) at 60—70° in the usual way. The product failed to crystallise but afforded a 2 : 4-*dinitrophenylhydrazone* as plates, m. p. 148—149°, from ethyl acetate–light petroleum (b. p. 60—80°) (Found: C, 54·6; H, 4·45; N, 14·9. $C_{17}H_{16}O_6N_4$ requires C, 54·85; H, 4·35; N, 15·05%). Cyclisation of the ester (20 g.) was best effected with 75% sulphuric acid (60 c.c.) at 50° for 24 hr. Crystallisation of the product (75%) from aqueous alcohol gave 4 : 7-dimethylcoumarin, m. p. 132° (Fries and Klostermann, *loc. cit.*, give m. p. 132°).

p-*Tolyl Acetoacetate.*—Prepared from *p*-cresol and diketen in the normal way and crystallised from chloroform–light petroleum (b. p. 40—60°), the *acetoacetate* (crude yield, 97%) formed clusters of needles, m. p. 65—66° (Found: C, 68·6; H, 6·35. $C_{11}H_{12}O_3$ requires C, 68·75; H, 6·3%). Heating of the ester (10 g.) with sulphuric acid (30 c.c.; 75—80%) at 50° for 24 hr. gave 4 : 6-dimethylcoumarin in 71% yield, m. p. 150—151°. The use of 98% acid at 20° gave only a 5% yield (Fries and Klostermann, *loc. cit.*, give m. p. 150°).

o-*Tolyl Acetatoacetate.*—This ester was obtained as an oil which gave a 2 : 4-*dinitrophenylhydrazone*, prisms, m. p. 125°, from *iso*propanol (Found: C, 55·25; H, 4·25; N, 14·7%). The ester was cyclised as for the *para*-compound, the solution poured into water, the product extracted with ether, the extracts washed with sodium hydroxide solution (10%), and the solvent evaporated. The coumarin (crude yield: 18—19%) formed needles, m. p. 112—113°, after recrystallisation from ethyl acetate–light petroleum (b. p. 60—80°) (Found: C, 75·65; H, 5·8. Calc. for $C_{11}H_{10}O_2$: C, 75·85; H, 5·8%). Since the material failed to give a precipitate with bromine in acetic acid [claimed by Desai (cf. Sethna and Shah, *loc. cit.*, p. 26) to be a diagnostic test for chromones], the product must be 4 : 8-dimethylcoumarin (Dey, *J.*, 1915, 1637, gives m. p. 118°) and not the isomeric 2 : 8-dimethylchromone (Simonis and Lehmann, *Ber.*, 1914, **47**, 697, give m. p. 115°).

2 : 3-*Xylyl Acetoacetate.*—Diketen (8·7 g.) was added dropwise during 0·5 hr. to an agitated, boiling solution of 2 : 3-xylenol (12·2 g.) in benzene (20 c.c.) containing triethylamine (0·2 c.c.). After being refluxed for 0·5 hr., the product was evaporated, giving the acetoacetate as an oil (21·4 g.). The ester (5 g.) was treated with sulphuric acid (15 c.c.; 98, 90, and 75%), and the mixtures set aside at room temperature for 24 hr. 4 : 7 : 8-*Trimethylcoumarin* (yields: 36, 60, and 63·5, respectively) formed needles, m. p. 145°, from aqueous ethanol (Found: C, 76·45; H, 6·5. $C_{12}H_{12}O_2$ requires C, 76·55; H, 6·45%).

2 : 4-*Xylyl Acetoacetate.*—The ester (an oil) was prepared from 2 : 4-xylenol and diketen as above. Cyclisation was carried out as with 2 : 3-xylyl acetoacetate, the products being isolated as described under the *o*-tolyl ester, giving the coumarin in 5, 48, and 24% yields, with sulphuric acid of 98, 90, and 75% concentration, respectively. 4 : 6 : 8-Trimethylcoumarin formed needles, m. p. 113—114°, from light petroleum (b. p. 60—80°) (Flynn and Robertson, *loc. cit.*, give m. p. 114—114·5°).

2 : 5-*Xylyl Acetoacetate.*—Prepared as previously described from 2 : 5-xylenol and diketen, the oily acetoacetate, on treatment with sulphuric acid (75, 80, or 98%) at 20° for 24 hr. and isolation as described under *o*-tolyl acetoacetate, failed to give any trace of coumarin.

3 : 4-*Xylyl Acetoacetate.*—Treatment of 3 : 4-xylenol with diketen as previously described afforded the *acetoacetate*, as needles, m. p. 45°, from light petroleum (b. p. 40—60°) (Found: C, 69·65; H, 6·65. $C_{12}H_{14}O_3$ requires C, 69·9; H, 6·85%). Treatment of the ester (5 g.) with sulphuric acid (15 c.c.; 80%) at room temperature for 24 hr., followed by isolation in the usual way, gave 4 : 6 : 7-trimethylcoumarin (86%), which recrystallised from aqueous alcohol as needles, m. p. 170—171° (Clayton, *loc. cit.*, gives m. p. 169—170°).

3 : 5-*Xylyl Acetoacetate.*—Acetoacetylation of 3 : 5-xylenol gave the *acetoacetate*, as needles, m. p. 48—49°, from light petroleum (b. p. 40—60°) (Found: C, 69·95; H, 6·9%). Cyclisation of the ester (5 g.) with sulphuric acid (90%; 15 c.c.) at 20° for 20 hr. gave a 49·5% yield of coumarin; more concentrated acid and shorter reaction times gave lower yields. 4 : 5 : 7-

Trimethylcoumarin formed plates, m. p. 183—184·5°, from ethanol (Clayton, *loc. cit.*, gives m. p. 175—176°).

α-*Naphthyl Acetoacetate.*—This *acetoacetate* was prepared by the standard method from α-naphthol and diketen in 86% yield; it crystallised as prismatic needles, m. p. 65—66·5°, from benzene–light petroleum (b. p. 40—60°) (Found: C, 73·5; H, 5·4. $C_{14}H_{12}O_3$ requires C, 73·65; H, 5·3%). Treatment of the ester (10 g.) with sulphuric acid (90%; 30 c.c.) at 20° for 24 hr. gave 4-methyl-7 : 8-benzocoumarin (6·4 g., 69·5%) which had m. p. 171°, after recrystallisation from ethanol (Appel, *J.*, 1935, 1031, gives m. p. 169·5—170·5°). Use of 80% sulphuric acid gave a quantitative yield of coumarin, m. p. 163—165°.

β-*Naphthyl Acetoacetate.*—Prepared from β-naphthol, the *acetoacetate* was obtained in 98% yield, and crystallised from ether–light petroleum ether (b. p. 60—80°) as plates, m. p. 80—81° (Found: C, 74·0; H, 5·3%). Both α- and β-naphthyl acetoacetates were more stable on storage than those derived from substituted phenols. Treatment of the ester (10 g.) with 98% or 80% sulphuric acid (30 c.c.) at room temperature afforded no significant amount of alkali-insoluble product, but with 90% acid a solid product (1·8 g.), m. p. 135—140°, was obtained. Repeated recrystallisation from ethanol did not raise this m. p. (Dey and Lakshminarayanan, *loc. cit.*, give m. p. 179° for the expected coumarin). The material (0·50 g.) with alcoholic sodium ethoxide and benzaldehyde afforded the styrylchromone (0·30 g.), m. p. 205—206° (Dey and Lakshminarayanan, *loc. cit.*, give m. p. 198°), and in acetic acid solution gave a precipitate with bromine in the same solvent indicating the presence of chromone (Desai, *loc. cit.*).

p-*Chlorophenyl Acetoacetate.*—The reaction of *p*-chlorophenol with diketen gave the *acetoacetate* (crude yield 95%) which formed needles, m. p. 54—55°, from chloroform–light petroleum (b. p. 40—60°) (Found: C, 56·85; H, 4·25. $C_{10}H_9O_3Cl$ requires C, 56·5; H, 4·25%). Treatment of the ester (10 g.) with sulphuric acid (75%; 30 c.c.) at room temperature overnight, and recrystallisation of the crude product from ethanol gave 6-chloro-4-methylcoumarin as needles (0·16 g.), m. p. 184—185° (Clayton, *loc. cit.*, gives m. p. 184—185°).

4-*Chloro*-m-*tolyl Acetoacetate.*—This ester solidified when first obtained but was unstable and soon liquefied. Treatment of the crude ester (10 g.) with sulphuric acid (75%; 30 c.c.) at 20° overnight and isolation gave a small yield of 6-chloro-4 : 7-dimethylcoumarin (0·10 g.), m. p. 208—210° after crystallisation from acetic acid (Chakravarti and Bannerjee, *loc. cit.*, give m. p. 208°).

4-*Chloro*-3 : 5-*xylyl Acetoacetate.*—The *acetoacetate*, obtained in 97% yield, formed needles, m. p. 68—70°, from light petroleum (b. p. 60—80°) (Found: C, 60·0; H, 5·05. $C_{12}H_{13}O_3Cl$ requires C, 59·9; H, 5·45%). Treatment with 75% sulphuric acid at room temperature overnight resulted in complete hydrolysis to 4-chloro-3 : 5-xylenol. The acetoacetate (30 g.) and sulphuric acid (98%; 100 c.c.) were heated at 90° for 1 hr. and then set aside for 2 days. The product was poured into water, and the precipitate washed with sodium hydroxide solution (10%), giving 6-chloro-2 : 5 : 7-trimethylchromone (9·2 g.), which crystallised from aqueous ethanol as needles, m. p. 145° (Adams and Mecorney, *loc. cit.*, give m. p. 145—146°). The styryl derivative, prepared by the method of Heilbron, Barnes, and Morton (*J.*, 1923, 2559), had m. p. 186—187° (Adams and Mecorney, *loc. cit.*, give m. p. 186—186·5°).

Reactions with Phosphoric Oxide.—(a) 4-*Chloro*-m-*tolyl acetoacetate.* The ester (10 g.) was heated with phosphoric oxide (10 g.) at 100° for 3 hr., and the dark, tarry product was then triturated with cold water and ether. The ethereal extract was well washed with 5% sodium hydroxide solution and with water, dried, and evaporated, giving a residue (1·1 g.), crystallisation of which from chloroform–light petroleum (b. p. 60—80°) gave 4-*chloro*-m-*tolyl* 2 : 6-*dimethyl*-γ-*pyrone*-3-*carboxylate* as prismatic needles, m. p. 90—91° (Found: C, 61·85; H, 4·6; Cl, 12·15. $C_{15}H_{13}O_4Cl$ requires C, 61·55; H, 4·45; Cl, 12·1%). When the ester (0·3 g.) was refluxed with hydrochloric acid (10%; 10 c.c.) for 2 hr., carbon dioxide was evolved; extraction of the product with ether (2 × 10 c.c.) and evaporation of the extract gave 4-chloro-*m*-cresol (1·3 g.), m. p. 66°. The aqueous layer was saturated with potassium hydroxide and re-extracted with ether (10 × 10 c.c.) (cf. Feist, *Annalen*, 1890, **257**, 291), and the solvent evaporated giving 2 : 6-dimethyl-γ-pyrone (1·1 g.), m. p. 136° (Feist, *loc. cit.*, gives m. p. 132°).

4-Chloro-*m*-cresol (2·1 g.) was heated at 100° for 0·5 hr. with *iso*dehydroacetyl chloride (1·86 g.); hydrogen chloride was rapidly evolved. The product was crystallised from benzene–light petroleum (b. p. 60—80°), giving 4-*chloro*-m-*tolyl* iso*dehydroacetate* (1·95 g.) as needles, m. p. 101—102° depressed on admixture with the above ester (Found: C, 61·5; H, 4·4; Cl, 12·0. $C_{15}H_{13}O_4Cl$ requires C, 61·55; H, 4·45; Cl, 12·1%).

(b) 3 : 4-*Xylyl acetoacetate.* The ester (15 g.) was heated with phosphoric oxide (15 g.) as described above and, on isolation, a solid product (4·6 g.), m. p. 96—102°, was obtained.

Crystallisation from benzene–light petroleum (b. p. 60—80°) gave 3 : 4-*xylyl* 2 : 6-*dimethyl-γ-pyrone*-3-*carboxylate* as needles, m. p. 109° (Found: C, 70·25; H, 6·0. $C_{16}H_{16}O_4$ requires C, 70·55; H, 5·9%). Hydrolysis as above gave 2 : 6-dimethyl-γ-pyrone.

(c) 2 : 5-*Xylyl acetoacetate*. The ester (10·3 g.) was heated with phosphoric oxide (7·5 g.) at 100° for 1 hr., more phosphoric oxide (5 g.) added, and heating continued for another hour. Isolation as above gave a solid residue (2·75 g.) which crystallised from aqueous methanol, giving 2 : 5-*xylyl* 2 : 6-*dimethyl-γ-pyrone*-3-*carboxylate* as plates, m. p. 101° (Found: C, 70·6; H, 6·0%). Hydrolysis gave 2 : 5-xylenol and 2 : 6-dimethyl-γ-pyrone.

(d) 2 : 4-*Xylyl acetoacetate*. The ester (11·7 g.) when heated with phosphoric oxide (12·5 g.) for 2 hr. at 100° and isolated as above gave a solid (4·5 g.), m. p. 105—109°, which, on crystallisation from aqueous methanol, gave 2 : 4-*xylyl* 2 : 6-*dimethyl-γ-pyrone*-3-*carboxylate* as prismatic needles, m. p. 116° (Found: C, 70·3; H, 5·8%).

The author thanks Messrs. A. R. Philpotts and W. Thain for light-absorption measurements recorded in the various Parts of this series, Professor E. R. H. Jones for gifts of materials used in the work described in Part III, the Agricultural Research Council under whose auspices Dr. Fenwick's work referred to in Part IV was done, and the Management of the British Industrial Solvents Division of the Distillers Company Limited for permission to publish these eight papers.

British Industrial Solvents, Development Dept.,
Hedon, Hull.

[*Received, August 1st*, 1953.]

---

*Densities of Some Binary Liquid Mixtures. Part II.**

By V. S. Griffiths.

[Reprint Order No. 4596.]

Densities of methanol–water and 1 : 4 dioxan–ethanol at 25° are reported, and in the latter system there are considerable differences from previously published data. Attempts to interpret molecular interaction from partial molal volume–mol. fraction curves are described.

This work extends that previously described in Part I * to two further systems.

Aqueous methanol solutions have been studied at various temperatures by many workers (*e.g.*, Klasen and Norlin at 15°, *Arkiv Kemi, Min., Geol.*, 1905—07, II, No. 27; International Critical Tables, 1929, at 20°; Subnis, Bhagwat, and Kanugo, *J. Indian Chem. Soc.*, 1948, **25**, 575, at 30°, 40°, and 50°) but accurate data at 25° over the entire concen-

1 : 4 *Dioxan–ethanol*

$C_4H_8O_2$ % (w/w)	*d*	Mean	$C_4H_8O_2$ % (w/w)	*d*	Mean	$C_4H_8O_2$ % (w/w)	*d*	Mean	$C_4H_8O_2$ % (w/w)	*d*	Mean
0	0·78506	0·78508	24·89	0·83532	0·83529	57·36	0·90867	0·90862	88·93	0·99360	0·99360
	0·78510			0·83525			0·90857			0·99359	
1·24	0·78753	0·78751	31·26	0·84887	0·84882	60·18	0·91567	0·91565	90·91	0·99970	0·99969
	0·78749			0·84878			0·91562			0·99968	
2·73	0·79046	0·79045	34·87	0·85669	0·85668	63·26	0·92332	0·92330	93·76	1·00808	1·00807
	0·79044			0·85666			0·92328			1·00805	
5·48	0·79589	0·79589	41·26	0·87082	0·87082	69·00	0·93864	0·93862	95·82	1·01483	1·01480
	0·79589			0·87081			0·93860			1·01478	
7·92	0·80076	0·80074	44·17	0·87740	0·87737	72·06	0·94630	0·94627	98·13	1·02202	1·02199
	0·80073			0·87735			0·94625			1·02196	
13·67	0·81238	0·81234	49·05	0·88860	0·88858	79·13	0·96532	0·96530	99·20	1·02518	1·02517
	0·81230			0·88857			0·96529			1·02516	
16·37	0·81780	0·81779	52·12	0·89588	0·89588	84·26	0·97989	0·97988	100·00	1·02806	1·02808
	0·81777			0·89587			0·97987			1·02810	
20·43	0·82611	0·82608									
	0·82605										

* Part I, *J.*, 1952, 1326.

Methanol–water

CH_3·OH % (w/w)	*d*	Mean	CH_3·OH % (w/w)	*d*	Mean	CH_3·OH % (w/w)	*d*	Mean	CH_3·OH % (w/w)	*d*	Mean
1·23	0·99465	0·99463	22·19	0·95985	0·95982	46·87	0·91827	0·91827	73·76	0·85811	0·85809
	0·99461			0·95979			0·91827			0·85808	
3·23	0·99100	0·99101	26·28	0·95319	0·95318	50·12	0·91203	0·91199	79·74	0·84431	0·84431
	0·99102			0·95318			0·91195			0·84430	
6·49	0·98566	0·98562	31·06	0·94524	0·94519	57·09	0·89789	0·89787	83·26	0·83599	0·83596
	0·98557			0·94515			0·89784			0·83593	
10·26	0·97878	0·97876	37·26	0·93445	0·93443	61·45	0·88707	0·88706	90·83	0·81463	0·81462
	0·97875			0·93441			0·88705			0·81460	
16·33	0·96878	0·96877	39·63	0·93162	0·93158	65·27	0·87865	0·87863	96·72	0·79649	0·79646
	0·96876			0·93154			0·87862			0·79643	
18·47	0·96607	0·96604	42·14	0·92700	0·92701	68·43	0·87144	0·87141	100·00	0·78655	0·78654
	0·96600			0·92703			0·87138			0·78653	

tration range appear to be scarce. Indeed the quoted values for the density of pure methanol at 25° range from 0·7864 to 0·7869 (Grinnell Jones and Forwalt, *J. Amer. Chem. Soc.*, 1938, **60**, **1683**; Gibson, *ibid.*, 1935, **57**, 1551; Vosburgh, Connell, and Butler, *J.*, 1933, 935; Timmermans "Physico-chemical Constants of Pure Organic Compounds," Elsevier, Amsterdam, 1950).

The densities of 1 : 4 dioxan–ethanol solutions have been determined by Hopkins, Yerger, and Lynch (*J. Amer. Chem. Soc.*, 1939, **61**, 2460) but since the value obtained for pure dioxan does not agree with that of the author (see Part I) it was felt necessary to reinvestigate the mixtures.

Consequently the two systems were carefully studied and the results are given in the annexed Table.

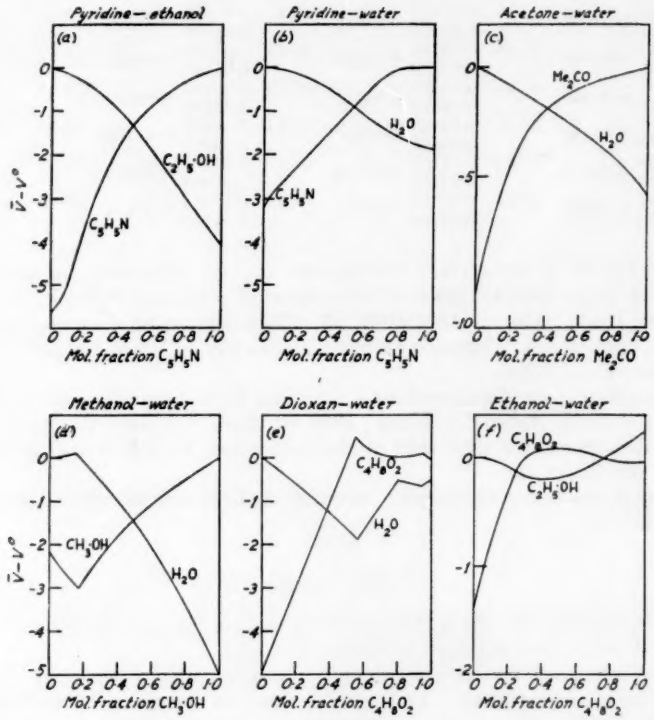
Discussion

The results obtained for the methanol–water system lie on a smooth curve and agree reasonably well with those obtained by Gibson (*loc. cit.*).

The values obtained for dioxan–ethanol mixtures indicate that the density varies continuously with concentration. In the lower range of dioxan concentrations the results agree with those of Hopkins, Yerger, and Lynch (*loc. cit.*) but in higher range there is some disagreement.

From the results obtained in this work partial molal volume–mol. fraction curves were constructed by the method described by Lewis and Randall ("Thermodynamics and the Free Energy of Chemical Substances," McGraw-Hill, 1923, p. 38). This graphical method of intercepts, whilst not being the most accurate for the determination of partial molal quantities, gives the essential shape of the curves. For convenience the diagram shows $\bar{V} - V^0$ (where $\bar{V}$ = partial molal volume, and V^0 = molal volume of the pure substance) plotted against the mol. fraction of one component. It can be seen that curves *a*, *b*, and *c* show certain similarities although the actual magnitude of the changes is greatest in the acetone–water system (*c*). Curve (*f*) shows that the partial molal volume of ethanol in dioxan solutions changes but little over the entire concentration range. However none of these curves show the sharp discontinuities exhibited by the methanol–water and dioxan–water systems. The former gives a curve very similar to the corresponding curve for the ethanol–water system (*idem*, *op. cit.*, p. 40) whilst the dioxan–water system (*e*) gives an unexpectedly complex curve (the break in the upper curve at approx. 0·84 mol. % of dioxan is not apparent on the scale used). Further, in this case, it must always be remembered that in the region where the curves show the most changes, the density is changing very slowly with concentration, and the experimental errors all but cover the variation. It was hoped that it might be possible to interpret the curves in terms of molecular association but no satisfactory explanation could be found. For example, if the type of curve obtained for ethanol–water and methanol–water systems be taken to indicate association then the same type of curve would be expected for the ethanol–dioxan

system since Freymann and Freymann (*Bull. Soc. chim.*, 1937, **4**, 944) and Errera and Sack (*Trans. Faraday Soc.*, 1938, **33**, 728) from infra-red measurements showed the characteristic OH frequency to be modified in such solutions. The latter authors also obtained



evidence of association in ethanol–pyridine mixtures, the curves of which are of an uncomplicated type.

Experimental.—The methods used were those described in Part I (*J.*, 1952, 1326).

Materials.—1 : 4-Dioxan and ethanol were purified by the methods described in Part I.

Commercial methanol was treated by the method of Bates, Mullaly, and Hartley (*J.*, 1923, 403) for the removal of aldehydes and ketones. The resulting alcohol was dried for several weeks over freshly-fired lime and fractionally distilled, the head and tail fractions being discarded. The middle fraction was distilled from metallic sodium immediately before use (Young and Fortey, *J.*, 1902, 717); it had b. p. 64·73°/760 mm.

BATTERSEA POLYTECHNIC, LONDON, S.W.11. [*Received, August 19th*, 1953.]

A Characteristic Infra-red Absorption of the Triphenylmethyl Group.

By S. Pinchas and David Samuel.

[Reprint Order No. 4622.]

The spectra of 13 compounds which contain the triphenylmethyl group all show a medium-strength band at about 1185 cm.$^{-1}$ and a weak band at about 1280 cm.$^{-1}$ which seem to be characteristic of this group. These bands are assigned to the stretching modes of vibration of the C–Ph bonds.

In connection with an investigation of rearrangements in the triphenylmethyl series a method was required by which this group could be easily identified. The infra-red spectra of a number of triphenylmethyl derivatives were therefore measured in the 800—1300 cm.$^{-1}$ region, and they all showed two bands, at 1179—1190 and 1270—1290 cm.$^{-1}$, which could not be attributed to any other group in these compounds, as seen by comparison with the spectra of similar substances not containing this group. It thus appears that these bands (see Table 1) are characteristic of the triphenylmethyl group. Besides the bands listed, the materials mentioned in Table 1 also show other bands in this region due to other parts of the molecule.

Table 1. *Position of* CPh_3 *bands in the* 1150—1300 *cm.*$^{-1}$ *region in various compounds.* (Cell thickness: 0·1 mm.; m = medium, w = weak.)

Compound	Concn.*	Bands (cm.$^{-1}$)	Compound	Concn.*	Bands (cm.$^{-1}$)
1. $CHPh_3$	0·20	1184 (m), 1290 (w)	8. $CPh_3{\cdot}CH_2{\cdot}CH_2Cl$	0·21	1187 (m), 1273 †
2. $CPh_3{\cdot}OH$	0·01 [a]	1179 (m), 1270 †	9. $CPh_3{\cdot}[CH_2]_3{\cdot}Cl$	0·19	1185 (m), 1286 (m)
3. $CClPh_3$	0·28	1184 (m), 1284 (w)	10. CPh_4	0·01 [a]	1186 (m), 1280 (w)
4. $CMePh_3$	0·27	1184 (m), 1282 (w)	11. $CPh_3{\cdot}CH_2{\cdot}CH_2Ph$	0·01 [a]	1186 (m), 1272 (w)
5. $CPh_3{\cdot}CH_2Cl$ ...	0·28	1185 (m), 1280 (w)	12. $CPh_3{\cdot}CHPh_2$	0·11	1187 (m), 1272 (w)
6. $CPh_3{\cdot}COCl$ ...	0·26	1190 (m), 1278 (w) [b]	13. $CPh_3{\cdot}CH(OH){\cdot}CHPh_2$	0·01 [a]	1184 (m), 1277 (w)
7. $CPh_3{\cdot}CH_2{\cdot}OEt$	0·15	1182 (m), 1279 (m)			

[a] A 2-mm. cell. [b] This band merges with a band at about 1265 cm.$^{-1}$.
* Concentrations are given in terms of g. per 1 c.c. of carbon disulphide. † Shoulder.

The infra-red absorption of triphenylmethane has been reported by Richards and Thompson (*Proc. Roy. Soc.*, 1949, *A*, **195**, 1) and Karagounis (*Helv. Chim. Acta*, 1951, **34**, 994), bands being recorded in this region at about 1190 and 1300 cm.$^{-1}$ for a carbon tetrachloride solution and at about 1179 cm.$^{-1}$ for the solid phase. Triphenyldeuteromethane in the same solvent also shows bands at about 1191 and 1283 cm.$^{-1}$ (Brown, Mighton, and Senkus, *J. Org. Chem.*, 1938, **3**, 62). For solid triphenylmethanol, Barnes, Gore, Liddel, and Williams ("Infra-red Spectroscopy," Reinhold Publ. Corp., New York, 1944, p. 59) report bands at about 1185 and 1280 cm.$^{-1}$. The spectra of *o*- and *m*-nitrotriphenylmethane ("Catalog of Infra-red Spectrograms," Sadtler & Son, Inc., Philadelphia; Nos. 1022, 1021) also show similar bands.

Sheppard (*Trans. Faraday Soc.*, 1950, **46**, 531) assigned the 1139—1159 cm.$^{-1}$ band, which appears in the spectra of *tert.*-butyl derivatives, to that mode of vibration which involves the symmetrical stretching of the C–Me bonds, and the 1230—1240 cm.$^{-1}$ band to the corresponding non-symmetrical mode of vibration. By analogy, the 1179—1190 cm.$^{-1}$ band in triphenylmethyl derivatives may be assigned to that mode of vibration in which all the phenyl groups move in phase in a stretching of the C–Ph bonds, and the 1270—1290 cm.$^{-1}$ band to a similar stretching vibration in which one phenyl group is out of phase. The relative intensity of these bands is in agreement with this assignment since, as with *tert.*-butyl derivatives, the symmetrical band is higher in intensity.

It is, however, noteworthy that, while the *tert.*-butyl halides show a decrease of about 50—70 cm.$^{-1}$ in the frequency of the first band and of about 10—20 cm.$^{-1}$ in that of the second band, relative to the values of these bands in the hydrocarbons (Simpson and Sutherland, *Proc. Roy. Soc.*, 1949, *A*, **199**, 169; 1200—1215 and 1250 cm.$^{-1}$), no such decrease was found in the triphenylmethyl compounds. A possible explanation may be that the mechanical coupling between the fourth substituent of the central carbon atom and the three $C–C_{ar.}$ bonds is not strong here and does not play a great part in determining

the frequency of these bands as does the analogous coupling in the case of the *tert.*-butyl derivatives (especially in relation to the first mode of vibration, see Sheppard, *loc. cit.*).

It should also be mentioned that, although *neo*pentane does not show the first band, corresponding to the symmetrical mode of vibration, at about 1200 cm.$^{-1}$ as do other hydrocarbon derivatives of *iso*butane (Simpson and Sutherland, *loc. cit.*), yet its analogue tetraphenylmethane (No. 10 of Table 1) does show it very clearly. This mode of vibration is not infra-red active in *neo*pentane on account of its perfect symmetry: it is therefore interesting that in the spectrum of tetraphenylmethane this band does appear.

The rise in the frequencies of the bands when C–Ph bonds are substituted for the C–Me bonds, *e.g.*, in CPh_3Cl, seems to be due to the effect of the neighbouring (aromatic) double bonds which tend to strengthen the other bonds of the doubly-bound carbon atom (Walsh, *Trans. Faraday Soc.*, 1947, **43**, 60). This rise is especially significant since the greater mass of a phenyl group would, *per se*, be expected to decrease the frequency.

On further examination of the infra-red absorption of similar compounds which do not contain the triphenylmethyl radical it appears that, although some of these compounds also show bands which are in or near the ranges assigned to this group, yet in most cases these compounds do not show both of the bands in the correct places and of the right intensity. If the special cases of the polar compounds triphenylmethanol and triphenylacetyl chloride (Table 1, Nos. 2 and 6) and the first member of the series,* triphenylmethane, are ignored in setting the limits for the characteristic ranges of absorption, the narrower ranges 1182—1187 and 1272—1286 cm.$^{-1}$ are obtained. These are more characteristic for the triphenylmethyl derivatives as can be seen from Table 2, which gives the absorption bands in this region of a number of similar compounds from which the triphenylmethyl group is absent.

TABLE 2. *Absorption bands of some compounds related to those of Table* 1 *in the* 1150—1300 *cm.*$^{-1}$ *region.*

Compound	Concn.*	Cell thickness (mm.)	Bands (cm.$^{-1}$)
14. $CHPh_2{\cdot}CH_2Ph$	0·24	0·1	1156, 1239
15. $CHPh_2Br$	0·01	2	1149, 1179, 1258
16. $CPh_2{:}CHPh$	0·17	0·1	1155, 1176, 1245, 1269
17. $CPh_2{:}CPhCl$	0·11	0·1	1154, 1177, 1231, 1287 (v. w.)
18. $CBr(CH_2Ph)_3$	0·01	2	1154, 1178, 1227, 1274 †
19. $C(OH)(CH_2Ph)_3$	0·01	2	1154, 1170, 1194 (w), 1208 (w), 1246, 1270

* See footnote, Table 1. † See footnote, Table 1.

It is, however, fully justified to assume that any substance which does not show a band at about 1180—1190 cm.$^{-1}$ does not contain a triphenylmethyl group. As the other band at about 1280 cm.$^{-1}$ is usually weak, a similar conclusion about this band seems unsafe. Hexaphenylethane, for instance, was observed (Karagounis, *loc. cit.*) to possess a band at about 1191 cm.$^{-1}$ in carbon tetrachloride solution but not one at about 1280 cm.$^{-1}$. Care should also be taken in comparing results obtained with different solvents, for a change of solvent is liable to cause small shifts in wave-lengths (see, *e.g.*, Williams, Hastings, and Anderson, *Analyt. Chem.*, 1952, **24**, 1911).

Experimental.—The instrument used in these measurements was a Perkin–Elmer Infra-red Spectrophotometer, Model 12C, equipped with a sodium chloride prism.

The authors are grateful to Professor E. D. Bergmann for samples of Nos. 10—14 inclusive, and to Dr. I. Dostrovsky for samples of Nos. 4, 5, 7, 8, 9, 16, and 17. Other compounds were prepared and purified by standard methods.

THE WEIZMANN INSTITUTE OF SCIENCE,
REHOVOTH, ISRAEL.

[*Received, August* 31*st*, 1953.]

* In the *tert.*-butyl series also, the first member, *iso*butane, behaves somewhat differently from the other members and shows bands at 1173 and 1277 cm.$^{-1}$ (American Petroleum Institute, Research Project 44, National Bureau of Standards Catalogue of Infra-red Data, Curve No. 439).

The Aggregation Tendencies of Acid Wool Dyes in Saline Solutions.

By K. N. Davies and J. Whetstone.

[Reprint Order No. 4744.]

The salting-out from aqueous solution of acid dyes by ammonium nitrate is discussed. The salting-out tendency is not related essentially to the proportion of solubilizing groups in the dye molecule, and various classes of dyes behave differently.

The generalisations as to the nature of the crystal-habit modification processes of inorganic salts with dyes contained in a preliminary notice by one of us (Whetstone, *Nature*, 1951, **168**, 663) were derived with the tacit assumption on the basis of results by Speakman and Clegg (*J. Soc. Dyers Col.*, 1934, **50**, 348) that, in view of the relatively high degree of sulphonation of most crystal-habit modifying dyes, single dye molecules rather than dye micelles were the active agents in the modifications. Evidence consistent with this assumption can now be presented from a direct study of the aggregation tendencies of a number of crystal-habit modifying dyes in ammonium nitrate solutions of various concentrations.

Experimental

The very convenient technique due to Fürth (*Kolloid Z.*, 1927, **41**, 300) using a "micro-diffusion cell" was ideally suited to the investigation since it is essential that the dye solutions under examination should contain electrolyte, to avoid errors due to the setting up of a diffusion potential. Dye concentrations of from 0·021 to 0·125% in ammonium nitrate solutions were studied. A brief account of the conclusions from the study of aggregation tendencies is given, since the dyes concerned were of the "acid wool" type rather than the "substantive cotton" type mostly studied, and the results may be of assistance to other workers in this field.

The radius r was obtained from the Stokes–Einstein equation $D = \boldsymbol{R}T/6\pi\eta\boldsymbol{N}r$, whereupon, with some assumptions, it was possible to calculate the approximate degrees of aggregation in ammonium nitrate solution of the dyes considered from the equation $A = 4\pi r^3 d\boldsymbol{N}/3M$, M being the molecular weight of the dye.

Owing to the uncertainty about the density, d, of the micelles it was difficult to calculate absolute aggregation tendencies from the average radii of dye aggregates deduced from the diffusion coefficients; the value of 1·5 was taken as an approximation to the densities in general. The degree of aggregation, A, was found always to increase on raising either the salt or the dye concentrations. However, stability to coagulation was found not to depend directly on degree of aggregation. For instance, the bisazo-dye EJ (2-naphthylamine-5 : 7-disulphonate→1-naphthylamine-7-sulphonate→2-naphthol-3 : 6-disulphonate), although aggregated to about five times as large a micelle as the monoazo-dye BD (1-naphthylamine-5-sulphonate→2-naphthol-3 : 6 disulphonate), was the more stable in 60% ammonium nitrate solutions.

The following Table shows the typical behaviour of the various dyes considered in ammonium nitrate solutions.

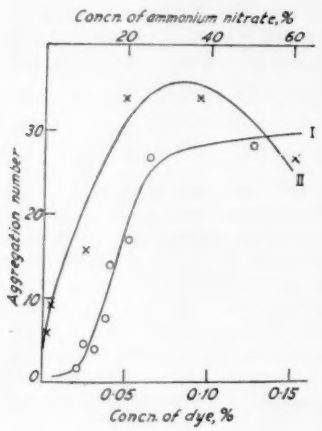
Aggregation behaviours of acid wool dyes of various types in ammonium nitrate solutions.

Dye	Concn., % of NH_4NO_3 solution	Concn., % of dye	A	Stability of solution
Acid Magenta	60	0·06	1·4	Perfectly stable
Amaranth	60	0·06	6·4	Rather unstable
,,	16·7	0·025	10	Stable
BD	16·7	0·025	3·2	Unstable
B2J	16·7	0·025	5·4	Very unstable
EJ	60	0·125	30	Unstable
,,	60	0·06	27	Rather unstable
,,	60	0·036	7·8	Stable
,,	60	0·021	1·7	Stable
,,	37	0·06	34	Stable
,,	10	0·06	16	Stable
,,	0	0·06	—	Perfectly stable

Discussion

The orientation of the solubilizing groups was considered by Speakman and Clegg to be important in deciding aggregation tendencies. Their observation that the higher the degree of sulphonation in proportion to the molecular weight, the lower appeared to be the aggregation tendency, does not accord with the aggregation behaviour of the azo-dye B2J (*p*-sulphanilic acid→2-naphthol-3 : 6-disulphonate) as compared with Amaranth (1-naphthylamine-4-sulphonate→2-naphthol-3 : 6-disulphonate) as judged by their solubilities in 60% ammonium nitrate solution or most other salt solutions; whereas Amaranth usually dissolves readily, the former dye is almost completely salted out. However, as measured in 16·7% solution, the aggregation of B2J is the lesser, which again shows that degree of aggregation and solubility are not directly related.

Acid Magenta, possibly the most notable habit modifier for ammonium nitrate, is strongly soluble and has a negligible aggregation tendency, the average molecular aggregation deduced at 0·06% dye concentration being only 1·4. It is noteworthy that of all the dyes studied Acid Magenta alone cannot form O–H–N hydrogen bonds, the only possibility being N–H–N bonds which are known to be weak (Rice, " Electronic Structure and Chemical Binding," McGraw-Hill, New York, 1940).



Plots of aggregation against concentration of dye in 60% ammonium nitrate and against concentration of ammonium nitrate solution containing 0·06% of dye EJ are shown in curves I and II respectively. Curve II shows a value of 0·66 for the aggregation in the purely aqueous solution of the dye. This is due to the error caused by the presence of a diffusion potential. It is seen that in both curves the aggregation approaches unity at low concentrations. This implies that the system considered is reversible, and that at each concentration there may be an equilibrium aggregate $\rightleftharpoons$ monomer. Since in the micro-diffusion cell there will be a concentration gradient, any aggregation number obtained in this investigation can only be an approximation especially in view of the other assumptions made. The postulate that monomeric dye molecules are responsible for crystal-habit modification is thus concordant with the observations.

The above findings have all been with dyes of a relatively high degree of sulphonation. A relatively small number of crystal-habit modifying dyes of low sulphonation are known which are strongly soluble in saline solutions (*e.g.*, sodium 1 : 4 : 5 : 8-tetra-aminoanthraquinone-2-sulphonate); their solubility is ascribable to other polar-solubilising groups than sulphonate. It is quite probable that weakly soluble dyes active as habit modifiers are adsorbed as micelles.

In view of the unpredictable effects of increasing dye concentration on its molecular aggregation, it is evident that the measurements of crystal-habit modifying powers of dyes based on a relatively small degree of habit change at low dye concentrations are incapable of extrapolation to yield reliable indications of habit-modifying power at high dye concentrations.

The authors express their gratitude to Dr. E. K. Pierpoint, who prepared many of the azo-dyes used in pure and salt-free condition by the method of Robinson and Mills (*Proc. Roy. Soc.*, 1931, *A*, **131**, 576).

Research Department, Imperial Chemical Industries Limited,
Nobel Division, Stevenston, Ayrshire. [*Received, October* 21*st*, 1953.]

The Preparation of 2-Substituted Fluoranthenes.

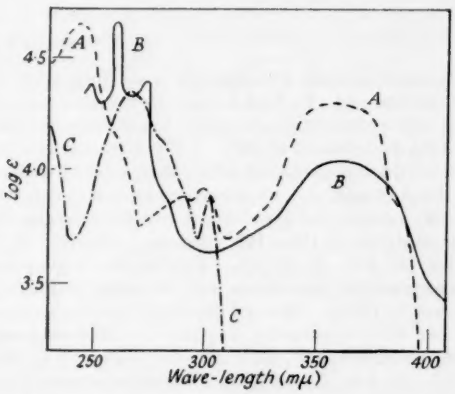
By Neil Campbell and J. F. K. Wilshire.

[Reprint Order No. 4702.]

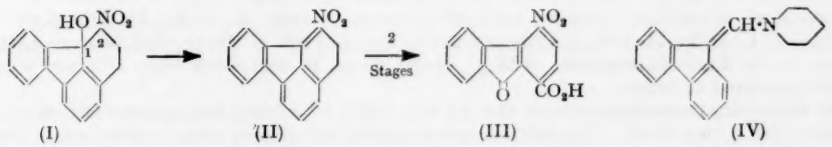
A synthesis of 2-nitrofluoranthene from 1 : 2 : 3 : 4-tetrahydrofluoranthene is described, thereby providing a general method for the preparation of 2-substituted fluoranthenes.

The few known 2-substituted fluoranthenes have been synthesised from fluorene (Bergmann and Orchin, *J. Amer. Chem. Soc.*, 1949, **71**, 1917; Campbell and Wang, *J.*, 1949, 1513; Forrest and Tucker, *J.*, 1948, 1137). We now record the first preparation of a 2-substituted fluoranthene from 1 : 2 : 3 : 4-tetrahydrofluoranthene, which is readily obtained by the reduction of fluoranthene. In an attempt to prepare a dinitrofluoranthene we nitrated tetrahydrofluoranthene with fuming nitric acid in acetic acid and obtained two products: a colourless solid (*A*), $C_{16}H_{13}O_3N$, and a deep orange solid (*B*), $C_{16}H_{11}O_2N$. *A* readily

A, 9-*Piperidinomethylenefluorene.*
B, 3 : 4-*Dihydro-2-nitrofluoranthene.*
C, 1 : 2 : 3 : 4-*Tetrahydrofluoranthene.*



yielded *B* by loss of a molecule of water, thereby suggesting that *A* is a nitro-alcohol and *B* a nitro-hydrocarbon. Oxidation of *B* by sodium dichromate and acetic acid gave β-(9-oxofluoren-1-yl)propionic acid and a compound which was subsequently proved to be 2-nitrofluoranthene. This strongly suggested that *A* is 1 : 2 : 3 : 4-tetrahydro-1-hydroxy-2-nitrofluoranthene (I) and (*B*) 3 : 4-dihydro-2-nitrofluoranthene (II). Confirmation of this was



(I) (II) (III) (IV)

afforded by dehydrogenation of *B* to 2-nitrofluoranthene (II; with a double bond in the 3 : 4-position) whose structure followed from its oxidation to 4-nitrofluorenone-1-carboxylic acid (III) which on decarboxylation yielded 4-nitrofluorenone identical with a sample kindly supplied by Professor J. W. Cook, F.R.S. The ultra-violet absorption spectrum of (II) should be similar to that of a fluorene derivative with a double bond at the 9-position. This was found to be so since the spectra of (II) and of 9-(piperidinomethylene)fluorene (IV) (Miller and Wagner, *J. Org. Chem.*, 1951, **16**, 279), though not identical, exhibited reasonable similarity (see Figure).

5-Bromo-1 : 2 : 3 : 4-tetrahydrofluoranthene reacted similarly with nitric acid, to give 5-bromo-1-hydroxy-1 : 2 : 3 : 4-tetrahydro-2-nitrofluoranthene and 5-bromo-3 : 4-dihydro-2-nitrofluoranthene, the latter on dehydrogenation yielding 5-bromo-2-nitrofluoranthene.

This preferential nitration in the alicyclic rather than in the aromatic nucleus is striking, especially since the 5-position in tetrahydrofluoranthene is susceptible to electophilic attack. Other examples of such nitrations are known and include that of 1: 4-dimethylnaphthalene to 4-methylnaphthyl-1-nitromethane (Robinson and Thompson, *J.*, 1932, 2015) and of 7-phenylacenaphthenone to the 7-nitro-compound (K. Henderson, Thesis, Edinburgh). Since these nitrations have all been effected in acetic acid it is tempting to ascribe the " abnormal " results to the formation of some nitrating agent such as acetyl nitrate. Against this, however, is the observation that side-chain nitration also occurs with other solvents such as nitromethane (see, *e.g.*, Robinson and Thompson, *loc. cit.*). A possible explanation, suggested by Titov (*Chem. Abs.*, 1948, **42**, 7262), is that under the conditions of our experiments (fuming nitric acid at 86°) the oxides of nitrogen which are formed may act an as anti-catalyst for nuclear nitration (see Hughes, Ingold, and Reed, *J.*, 1950, 2432) whilst promoting nitration and oxidation of the reduced ring.

As was expected the spectrum of 1 : 2 : 3 : 4-tetrahydrofluoranthene was found to resemble that of fluorene (see Figure).

Experimental

Chromatographic experiments were done with B.D.H. chromatographic alumina.

Nitration of 1 : 2 : 3 : 4-*Tetrahydrofluoranthene.*—Fuming nitric acid (*d* 1·48; 7·17 ml., 0·15 mole) was added dropwise to the tetrahydro-compound (20·6 g., 0·1 mole) in glacial acetic acid (200 ml.) maintained at 80°. After 1 hr. the solution was cooled and poured into iced water. The product was extracted with ether, washed with aqueous sodium carbonate, then with water, and dried (Na_2SO_4). Evaporation gave a syrup which when triturated with benzene yielded 1 : 2 : 3 : 4-*tetrahydro*-1-*hydroxy*-2-*nitrofluoranthene*, colourless octahedra (from chlorobenzene or acetic acid), m. p. 192—193° (decomp.) (Found: C, 71·5; H, 4·8; N, 5·3. $C_{16}H_{13}O_3N$ requires C, 71·9; H, 4·9; N, 5·2%). The filtrate on evaporation gave a red syrup which was dissolved in benzene–light petroleum and chromatographed (for details see J. F. K. Wilshire, Thesis, Edinburgh, 1952). More of the hydroxynitro-compound was thus obtained (total yield, 7·13 g.) together with, apparently, impure 3 : 4-dihydro-2-nitrofluoranthene (5·82 g.), elongated orange prisms (from ethanol), m. p. 92—94° (Found: C, 76·3; H, 4·4; N, 6·1. Calc. for $C_{16}H_{11}O_2N$: C, 77·1; H, 4·4; N, 5·6%). The nitro-compound was readily obtained from the hydroxynitro-compound by dehydration with acetic anhydride or acetic acid containing a few drops of sulphuric acid.

Structure of 3 : 4-*Dihydro*-2-*nitrofluoranthene.*—The nitro-compound (1·72 g.) was boiled for 3 hr. with sodium dichromate (10 g.) in glacial acetic acid (75 ml.). Half of the acetic acid was distilled off and the residual solution poured into dilute sulphuric acid. The acidic solution was shaken with benzene and ether, and the extract washed with water and then with sodium carbonate solution. Acidification of the sodium carbonate layer gave β-(9-oxofluoren-1-yl)-propionic acid (0·27 g.), yellow plates (from benzene–light petroleum), m. p. 134—136° undepressed when admixed with an authentic sample (Found: C, 75·5; H, 4·7. Calc. for $C_{16}H_{12}O_3$: C, 76·2; H, 4·8%). The non-acidic material left in the original benzene extract proved to be 2-nitrofluoranthene (0·58 g.) giving no m. p. depression when admixed with a sample prepared as below.

3 : 4-Dihydro-2-nitrofluoranthene (8·0 g.) was boiled in sulphur-free xylene (120 ml.) with chloranil (16 g.) for 23 hr. The solution was decanted and diluted with benzene, washed with 5% aqueous sodium hydroxide (3 × 200 ml.), once with 10% sodium hydroxide, and finally with water. The dried (Na_2SO_4) solution was evaporated to small volume, and light petroleum (b. p. 80—100°) was added. The solution was boiled with charcoal and filtered hot and on cooling deposited 2-*nitrofluoranthene* (4·75 g.), yellow elongated prisms, m. p. 151—153° (Found: C, 77·9; H, 3·5; N, 5·7. $C_{16}H_9O_2N$ requires C, 77·7; H, 3·6; N, 5·7%). 2-Nitrofluoranthene (2·0 g.) was boiled for 20 hr. with glacial acetic acid (150 ml.) and sodium dichromate (40 g.). The solution was evaporated to half-volume and poured into dilute sulphuric acid. The mixture was shaken with chloroform and the chloroform layer extracted with 5% aqueous potassium carbonate. The potassium salt which separated and the alkaline extract, on acidific-

ation, yielded *4-nitrofluorenone-1-carboxylic acid* (0·96 g.), yellow elongated prisms, m. p. 213—214° (Found: C, 62·4; H, 2·3; N, 5·1. $C_{14}H_7O_5N$ requires C, 62·4; H, 2·6; N, 5·2%). It forms a *methyl* ester, hexagonal prisms (from methanol), m. p. 163·5—165° (Found: C, 63·3; H, 2·8; N, 4·9. $C_{15}H_9O_5N$ requires C, 63·6; H, 3·2; N, 5·0%). Decarboxylation of the acid (0·25 g.) with quinoline (10 ml.) and copper bronze at 180° for 1 hr. gave a neutral product which was chromatographed in benzene on a column 6″ × ½″. Development with light petroleum gave a pale yellow zone of 4-nitrofluorenone, yellow needles (from ethanol), m. p. 174—175°, undepressed when admixed with an authentic sample (Found: C, 69·0; H, 2·8; N, 6·1. Calc. for $C_{13}H_7O_3N$: C, 69·3; H, 3·1; N, 6·2%). Reduction with concentrated hydrochloric acid and reduced iron powder gave 4-aminofluorenone, red plates (from aqueous ethanol), m. p. 137—139° (lit., 138°) (Found: C, 78·9; H, 4·7. Calc. for $C_{13}H_9ON$: C, 80·0; H, 4·7%).

2-Nitrofluoranthene (1·6 g.) was boiled in ethanol (150 ml.) for 2 hr. with concentrated hydrochloric acid (10 ml.) and reduced iron powder (2 g.). The solution was poured into water and extracted with ether which on evaporation gave 2-aminofluoranthene, greenish-yellow needles (1·1 g.), m. p. 134—136° (lit., 133—134°) (Found: C, 89·0; H, 5·3. Calc. for $C_{16}H_{11}N$: C, 88·6; H, 5·1%). It forms an *acetyl* derivative, elongated prisms (from acetic acid), m. p. 254—255° (Found: C, 83·4; H, 5·2; N, 5·4. $C_{18}H_{13}ON$ requires C, 83·4; H, 5·0; N, 5·4%), and a *benzoyl* derivative, needles (from acetic acid), m. p. 237—238° (Found: N, 4·8. $C_{23}H_{15}ON$ requires N, 4·4%).

5-Bromo-2-nitrofluoranthene.—By a similar series of reactions 5-bromo-1 : 2 : 3 : 4-tetrahydrofluoranthene (11·5 g.) was converted into *5-bromo-1 : 2 : 3 : 4-tetrahydro-1-hydroxy-2-nitrofluoranthene* (4·88 g.), hexagonal prisms (from acetic acid), m. p. 163—164° (Found: C, 55·8; H, 3·5; N, 3·8; Br, 22·9. $C_{16}H_{12}O_3NBr$ requires C, 55·5; H, 3·5; N, 4·1; Br, 23·1%) and *5-bromo-3 : 4-dihydro-2-nitrofluoranthene* (2·07 g., crude), orange needles (from benzene–ethyl acetate), m. p. 181—183° (Found: N, 4·4; Br, 24·9. $C_{16}H_{10}O_2NBr$ requires N, 4·3; Br, 24·4%). The pure dihydro-compound (0·15 g.) was boiled in nitrobenzene (15 ml.) with chloranil (0·12 g.) for 48 hr. The nitrobenzene was removed by steam-distillation and the product dissolved in benzene which was then washed with 10% aqueous sodium hydroxide, twice with more dilute sodium hydroxide, then with water, and finally dried (Na_2SO_4). The benzene solution was reduced and passed down a column 6″ × ½″. Development with benzene gave a bright yellow band which yielded a crystalline solid (0·125 g.). Successive crystallisations from benzene–acetic acid, ethyl acetate, and acetic acid gave somewhat impure *5-bromo-2-nitrofluoranthene*, orange needles, m. p. 165—168° (Found: C, 58·2; H, 2·6; N, 4·3; Br, 24·3. $C_{16}H_8O_2NBr$ requires C, 58·9; H, 2·5; N, 4·3; Br, 24·5%).

Spectroscopic Measurements.—The ultra-violet spectra of the following substances were measured by means of a Hilger Barfit Medium Spectrograph. The solvent was spectrographically pure *cyclo*hexane (B.D.H. Ltd.). Log ε is given in parentheses. 2-Nitro-3 : 4-dihydrofluoranthene: 248 (4·4), 261 (4·66), 270 (4·38), and 365 mμ (4·04). 5-Bromo-2-nitro-3 : 4-dihydrofluoranthene: 266 (4·53), 276 (4·61), 289 (4·26), and 368 mμ (3·92). The bathochromic influence of the bromine atom is thereby demonstrated. 1 : 2 : 3 : 4-Tetrahydrofluoranthene: 266 (4·33), 280 (4·13) (inflection), and 303 mμ (3·88). These bands correspond to the three main absorption bands of fluorene of nearly the same wave-lengths (Askew, *J.*, 1935, 512; Mayneord and Roe, *Proc. Roy. Soc.*, 1937, A, **158**, 640).

Thanks are expressed to the University of Edinburgh for the award of a post-graduate studentship to one of us (J. F. K. W.) and to the Anglo-Iranian Oil Company, Limited, for a grant.

UNIVERSITY OF EDINBURGH. [*Received, October 6th*, 1953.]

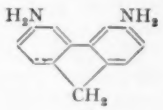
3 : 6-*Disubstituted Fluorenes. Part II.* The Preparation of* 3 : 6-*Diaminofluorene from Fluorene, and the Attempted Internuclear Cyclisation of Derivatives of* 4 : 4′-*Diaminodiphenylmethane.*

By A. Barker and C. C. Barker.

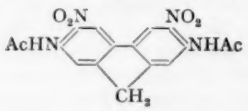
[Reprint Order No. 4792.]

3 : 6-Diaminofluorene is prepared from fluorene in eight stages, and its constitution is established. Attempts to prepare this amine, or its derivatives, from derivatives of 4 : 4′-diaminodiphenylmethane succeeded only with 4 : 4′-bisdimethylaminobenzophenone-2-diazonium sulphate which gave 3 : 6-bisdimethylaminofluorenone.

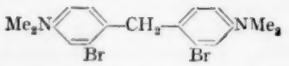
As a result of the failure of attempts to prepare 3 : 6-diaminofluorene (I) from 3 : 3′-diaminodiphenyl (Part I*) its preparation from fluorene was examined. Nitration of 2 : 7-diacetamidofluorene gave the 3 : 6-dinitro-derivative (II) which failed, however, to give 3 : 6-dinitrofluorene by successive deacetylation, tetrazotisation, and treatment with ethanol; a sparingly soluble, red product which resisted purification was obtained. Campbell and Stafford (*J.*, 1952, 299) obtained a similar product when attempting to deaminate 2-amino-3-nitrofluorene, and it seems that this is determined by the methylene group since the deamination of 4 : 4′-diamino-2 : 2′-dinitrodiphenylmethane encounters similar difficulties, whereas 2 : 7-diamino-3 : 6-dinitrofluorenone is deaminated normally.



(I)



(II)



(III)

Nitration of 2 : 7-diacetamidofluorenone gave the 3 : 6-dinitro-derivative which was identical with oxidised 2 : 7-diacetamido-3 : 6-dinitrofluorene. Deacetylation and deamination of this fluorene proceeded normally but gave a crude product from which 3 : 6-dinitrofluorenone could be isolated only by sublimation at 250—260°/10^{-4} mm. Reduction of this nitro-compound with stannous chloride gave yellow 3 : 6-diaminofluorenone which was reduced by the Huang-Minlon–Wolff–Kishner reaction to 3 : 6-diaminofluorene, the yield from fluorene amounting to 10%.

The structure of 3 : 6-diaminofluorenone, and hence of its precursors, was established by converting the base into 3 : 6-dichloro- and 3 : 6-dibromo-fluorenone by the Sandmeyer reaction. Huntress and Cliff (*J. Amer. Chem. Soc.*, 1933, **55**, 2566) prepared the former from 5 : 5′-dichlorodiphenic anhydride, and Courtot and Kronstein (*Chim. et Ind.*, Special No., 1941, **45**, 72) prepared the latter from 3 : 6-dibromophenanthraquinone. Attempts to convert 3 : 6-diaminofluorene into 3 : 6-dibromofluorene by the Sandmeyer reaction gave 3 : 6-dibromofluorenone and unidentified substances, but 3 : 6-diaminofluorenone is a useful precursor and gave 3 : 6-dihydroxyfluorenone without difficulty.

A more attractive route to 3 : 6-diaminofluorene or its derivatives was offered by the internuclear cyclisation of derivatives of 4 : 4′-diaminodiphenylmethane, but considerable difficulties were encountered. Thus, 2 : 2′-dibromo-4 : 4′-bisdimethylaminodiphenylmethane (III) gave only 4 : 4′-bisdimethylaminodiphenylmethane (33%) and starting material (54%) when heated with palladised calcium carbonate, hydrazine, and potassium hydroxide, although Busch and Weber (*J. pr. Chem.*, 1936, **146**, 47) obtained low yields of 2 : 7-diaminofluorene from 5 : 5′-diamino-2 : 2′-dibromodiphenylmethane by this method. 4 : 4′-Bisdimethylamino-2 : 2′-di-iododiphenylmethane also gave no 3 : 6-bisdimethylaminofluorene when heated with copper powder. 4 : 4′-Diacetamido- and 4 : 4′-bisdimethylamino-diphenylmethane-2-diazonium sulphates failed to cyclise when decomposed by heat or copper powder, but 4 : 4′-bisdimethylaminobenzophenone-2-diazonium sulphate gave

* Part I, *J.*, 1953, 2034.

3 : 6-bisdimethylaminofluorenone (12%) when heated in 88% sulphuric acid; the use of 10% acid gave only 4 : 4'-bisdimethylamino-2-hydroxybenzophenone. A similar effect was observed by Guyot and Haller (*Bull. Soc. chim.*, 1901, **25**, 750) when cyclising 4 : 4' : 4''-trisdimethylaminotriphenylmethane-2-diazonium sulphate, and Nunn, Schofield, and Theobald (*J.*, 1952, 2800) found that 5-nitrobenzophenone-2-diazonium sulphate cyclised only in the presence of high concentrations of sulphuric acid.

Experimental

2 : 7-*Diamino*-3 : 6-*dinitrofluorene*.—2 : 7-Diacetamidofluorene (10 g.; cf. Morgan and Thomason, *J.*, 1926, 2691) was added during 10 min. to a stirred mixture of nitric acid (95%; 100 c.c.) and acetic anhydride (24 c.c.) at −12° (±2°). After 2 more minutes the solution was poured into ice-water, and the solid was removed, washed until acid-free, dried, extracted with hot acetic acid to remove material which inhibited crystallisation, and crystallised from nitrobenzene (100 c.c.), giving 2 : 7-*diacetamido*-3 : 6-*dinitrofluorene* (11·0 g.) as yellow needles which decomposed slowly above 290° (Found: C, 54·5; H, 3·9; N, 14·2. $C_{17}H_{14}O_6N_4$ requires C, 55·1; H, 3·8; N, 15·1%). A mixture of the nitro-compound (6·0 g.), sulphuric acid (24 c.c.), and water (6·0 c.c.) was kept at 100° for 40 min., the solution was poured on ice, and the solid washed until acid-free, dried, and crystallised from aniline, giving red-brown crystals of 2 : 7-*diamino*-3 : 6-*dinitrofluorene* which did not melt at 360° (Found: C, 54·4; H, 3·6; N, 20·6. $C_{13}H_{10}O_4N_4$ requires C, 54·5; H, 3·5; N, 19·6%).

2 : 7-*Diacetamidofluorenone*.—Fluorene, technical grade twice crystallised from acetic acid, was oxidised to fluorenone (59%) by Huntress, Hershberg, and Cliff's method (*J. Amer. Chem. Soc.*, 1931, **53**, 2720), and the ketone was nitrated to 2 : 7-dinitrofluorenone (73%) as directed by Schmidt, Retzlaff, and Haid (*Annalen*, 1912, **390**, 224). The dinitro-compound (162 g.) was added cautiously to a solution of hydrated stannous chloride (1100 g.) in a mixture of concentrated hydrochloric acid (900 c.c.) and acetic acid (1600 c.c.), and the suspension was stirred and refluxed for 1 hr. The mixture was cooled, and the solid removed and washed with concentrated hydrochloric acid, then with water until the filtrate just became violet. The residue was dissolved in boiling water, the filtered solution basified with sodium hydroxide, and the precipitate washed with water, dried, and crystallised from nitrobenzene (1250 c.c.), giving 2 : 7-diaminofluorenone (108 g.), m. p. 284—286°. Schmidt, Retzlaff, and Haid (*loc. cit.*) employed tin and hydrochloric acid and gave m. p. 290°; Courtot (*Ann. Chim.*, 1930, **14**, 87) used ethanolic ammonium sulphide, but attempts to repeat his work gave crystalline, brown substances, m. p. 245—250°.

Acetylation of the amine with acetic anhydride in acetic acid gave pinkish-red 2 : 7-*diacetamidofluorenone* (94%), m. p. 348—349° (from nitrobenzene) (Found: C, 68·9; H, 5·0; N, 9·5. $C_{17}H_{14}O_3N_2$ requires C, 69·4; H, 4·8; N, 9·5%).

2 : 7-*Diamino*-3 : 6-*dinitrofluorenone*.—(*a*) 2 : 7-Diacetamidofluorenone (128 g.) was added during 10 min. to a stirred mixture of nitric acid (95%; 1550 c.c.) and acetic anhydride (350 c.c.) at 0—5°. After 12 more minutes the solution was poured into ice-water, and the solid washed until acid-free, and dried, giving 2 : 7-*diacetamido*-3 : 6-*dinitrofluorenone* (150 g.), which crystallised from nitrobenzene in orange needles, m. p. 335—336° (Found: C, 53·2; H, 3·1; N, 15·0. $C_{17}H_{12}O_7N_4$ requires C, 53·1; H, 3·1; N, 14·6%). Hydrolysis of this compound as described for its fluorene analogue gave the corresponding *amine* as a bronze-coloured powder which did not melt at 400°, sparingly soluble in hot pyridine, hot aniline, or hot nitrobenzene (Found: C, 52·3; H, 2·5; N, 19·5. $C_{13}H_8O_5N_4$ requires C, 52·0; H, 2·7; N, 18·7%).

(*b*) A solution of 2 : 7-diacetamido-3 : 6-dinitrofluorene (1·4 g.) and chromium trioxide (2·0 g.) in acetic acid (50 c.c.) was refluxed for 3 hr., and cooled, and the separated solid (0·65 g.) dried and crystallised from nitrobenzene, giving 2 : 7-diacetamido-3 : 6-dinitrofluorenone, m. p. and mixed m. p. with a sample from (*a*) 335—336°.

3 : 6-*Dinitrofluorenone*.—Nitrosylsulphuric acid, prepared from sodium nitrite (36 g.) and sulphuric acid (200 c.c.), was added at 0—5° during 15 min. to a solution of 2 : 7-diamino-3 : 6-dinitrofluorenone, obtained by hydrolysing the diacetyl compound (65 g.) with water (123 c.c.) and sulphuric acid (227 c.c.). After 40 min. the solution was run into hypophosphorous acid (50%; 835 c.c.) at 0—5° and kept at that temperature overnight. Water (1500 c.c.) was added and the separated solid (44 g.) washed until acid-free, dried, sublimed at 250—260°/10^{-4} mm., then crystallised from nitrobenzene (120 c.c.), giving yellow leaflet of 3 : 6-*dinitrofluorenone* (22 g.), m. p. 342—345°, raised to m. p. 344—346° when chromatographed in pyridine on activated alumina (Found: C, 57·8; H, 2·3; N, 10·2. $C_{13}H_6O_5N_2$ requires C, 57·8; H, 2·3; N, 10·4%).

The sublimation was slow, 10 g. of sublimate collecting in 12 hr. on a condensing surface of 10 in.^{2}.

3 : 6-*Diaminofluorenone.*—Reduction of 3 : 6-dinitrofluorenone (m. p. 342—345°; 40 g.) by the procedure used with 2 : 7-dinitrofluorenone gave a crude product which was purified by passing its filtered solution in pyridine down an alumina column (16 × 2·5 cm.). The eluate (1500 c.c.) was evaporated to 170 c.c., and water (340 c.c.) slowly added, giving 3 : 6-*diaminofluorenone* (27 g.), m. p. 249—251°, sparingly soluble in benzene, alcohol, or acetone, and crystallising from pyridine–alcohol in small orange needles, m. p. 252—253° (Found: C, 74·2; H, 4·7; N, 13·1. $C_{13}H_{10}ON_2$ requires C, 74·3; H, 4·8; N, 13·3%).

3 : 6-*Diaminofluorene.*—A stirred mixture of 3 : 6-diaminofluorenone (2·0 g.), trimethylene glycol (14 c.c.), hydrazine hydrate (100%; 1 c.c.), and sodium hydroxide (1·0 g.) was heated to 165° during 10 min.; a deep red precipitate was formed. The temperature was then raised to 200° during 30 min., to 205° during 1 hr., and to 215° during 3 hr. The clear amber-coloured solution was cooled and diluted with water (30 c.c.), and the crystalline product sublimed at 190—200°/10^{-3} mm. and crystallised from aniline (4·5 c.c.), giving long, pale yellow needles of 3 : 6-*diaminofluorene* (1·47 g.), m. p. 260—262°, sparingly soluble in hot ethanol, acetone, or benzene, more soluble in hot pyridine, readily soluble in hot aniline and hot nitrobenzene (Found: C, 78·7; H, 6·0; N, 14·2. $C_{13}H_{12}N_2$ requires C, 79·6; H, 6·1; N, 14·3%).

3 : 6-*Dihydroxyfluorenone.*—Nitrosylsulphuric acid, from sodium nitrite (1·05 g.) and sulphuric acid (10 c.c.), was added dropwise to a solution of 3 : 6-diaminofluorenone (1·6 g.) in sulphuric acid (10 c.c.), and the solution was kept for 20 min., then poured on ice (100 g.). After 2 hr. the excess of nitrous acid was destroyed with sulphamic acid, the solution was boiled for 10 min. and cooled, the precipitate dissolved in aqueous alkali, the deep red solution filtered and acidified, and the product sublimed at 210/10^{-4} mm., then crystallised from ethanol (15 c.c.), giving deep yellow, feathery needles of 3 : 6-*dihydroxyfluorenone*, m. p. 345—348° (decomp.) (Found: C, 72·9; H, 3·6. $C_{13}H_8O_3$ requires C, 73·6; H, 3·8%).

3 : 6-*Dichloro- and* 3 : 6-*Dibromo-fluorenone.*—3 : 6-Diaminofluorenone was tetrazotised in hydrochloric acid and treated with cuprous chloride; the product was sublimed at 210°/10^{-4} mm. and crystallised from benzene, giving 3 : 6-dichlorofluorenone (50%) as yellow needles, m. p. 299—301° (Found: C, 62·7; H, 2·4; Cl, 28·3. Calc. for $C_{13}H_6OCl_2$: C, 62·7; H, 2·4; Cl, 28·5%). Huntress and Cliff (*loc. cit.*) give m. p. 301°. The oxime had m. p. 250—252° (Found: C, 59·0; H, 3·0; N, 5·2. Calc. for $C_{13}H_7ONCl_2$: C, 59·1; H, 2·7; N, 5·3%), Huntress and Cliff (*loc. cit.*) give m. p. 243·5°. 3 : 6-Dibromofluorenone, prepared in an analogous manner, formed small, yellow leaflets (from benzene–xylene), m. p. 323—324°. Courtot and Kronstein (*loc. cit.*) give m. p. 321° (Found: Br. 47·0. Calc. for $C_{13}H_6OBr_2$: Br, 47·3%). The oxime had m. p. 262—263° (Found: N, 3·9. Calc. for $C_{13}H_7ONBr_2$: N, 4·0%). Courtot and Kronstein (*loc. cit.*) give m. p. 262—263°.

2-*Acetamido*-4 : 4′-*bisdimethylaminobenzophenone.*—Nitration of 4 : 4′-bisdimethylaminodiphenylmethane gave the 2-nitro-derivative (76%), m. p. 96—98°, removal of the 2 : 2′-dinitro-derivative by fractional basification replacing the ethanol extraction used by Ullmann and Marie (*Ber.*, 1901, **34**, 4314), who give m. p. 95°. Reduction of the nitro-compound in 90% ethanol with iron pin-dust and hydrochloric acid, followed by acetylation, gave 2-acetamido-4 : 4′-bisdimethylaminodiphenylmethane (70%), m. p. 140—141°. Kliegl (*Ber.*, 1906, **39**, 1273) gives m. p. 138°. Oxidation of this amine with chloranil gave 2-acetamido-4 : 4′-bisdimethylaminobenzophenone (78%), m. p. 165—167°. Kliegl (*loc. cit.*) gives m. p. 162°.

3 : 6-*Bisdimethylaminofluorenone.*—The aforementioned ketone (5·0 g.) was hydrolysed with sulphuric acid (25·5 c.c.) and water (9·0 c.c.) at 100° for 1 hr. and the amine suspension was diazotised at 0° with nitrosylsulphuric acid prepared from sodium nitrite (1·08 g.) and sulphuric acid (12·5 c.c.). After being kept overnight at room temperature the diazonium solution was kept at 70° until a sample gave no red colour with water. The product was precipitated with ammonia, dried, and eluted from a short alumina column with dry pyridine until a sample of the eluate, diluted with ethanol, gave no orange-red fluorescence in ultra-violet light. The pyridine was removed, and the residue crystallised from ethanol (15 c.c.) containing potassium hydroxide (1·0 g.), giving deep orange crystals of 3 : 6-*bisdimethylaminofluorenone* (0·5 g.), m. p. 249—250° (Found: C, 76·0; H, 6·8; N, 9·8. $C_{17}H_{18}ON_2$ requires C, 76·7; H, 6·8; N, 10·5%). Attempted cyclisation in 10% sulphuric acid gave pale yellow 4 : 4′-*bisdimethylamino*-2-*hydroxybenzophenone*, m. p. 172°, insoluble in aqueous but soluble in ethanolic potassium hydroxide (Found: C, 71·7; H, 7·1; N, 9·6. $C_{17}H_{20}O_2N_2$ requires C, 71·8; H, 7·1; N, 9·8%).

4 : 4′-*Diacetamido*-2-*aminodiphenylmethane.*—4 : 4′-Diaminodiphenylmethane was nitrated as described by Epstein (D.R.-P. 139,989; *Chem. Zentr.*, 1903, I, 798) but separation of the

2-nitro- from the 2 : 2′-dinitro-derivative by fractional basification of the sulphates, nitrates, or chlorides failed because partial neutralisation precipitated the salts. By dissolving the bases in acetic acid and adding 4 vol. of water the dinitro-compound was precipitated, leaving in solution 4 : 4′-diamino-2-nitrodiphenylmethane (60%), m. p. 88·5—90° (from ethanol) (Found : N, 17·7. Calc. for $C_{13}H_{13}O_2N_3$: N, 17·3%). Epstein gives m. p. 100—101°. The *diacetyl* derivative (94%), m. p. 220—223°, formed cream-coloured crystals from aqueous acetic acid (Found : C, 62·3; H, 5·0; N, 12·9. $C_{17}H_{17}O_4N_3$ requires C, 62·4; H, 5·2; N, 12·8%). A suspension of this nitro-compound (7·8 g.) in ethanol (95 c.c.) was stirred with hydrochloric acid (25 c.c.) and hydrated stannous chloride (21 g.) for 20 hr. at 20°, then kept overnight at 0°. White amine stannichloride separated and was collected, washed with a little ethanol, suspended in water, and decomposed with hydrogen sulphide. The mixture was filtered at 40° and the residue extracted with boiling wate r(4 × 100 c.c.), giving a solution which deposited the aminehydrochloride on cooling. Basification with ammonia gave 4 : 4′-*diacetamido*-2-*aminodiphenylmethane* (2·2 g.), m. p. 226—227° (needles from methanol) (Found : C, 68·1; H, 6·4; N, 13·9. $C_{17}H_{19}O_2N_3$ requires C, 68·6; H, 6·5; N, 14·1%).

4 : 4′-*Bisdimethylamino*-2 : 2′-*di-iodo- and* 2 : 2′-*Dibromo*-4 : 4′-*bisdimethylamino-diphenylmethane.*—*m*-Iodo-*NN*-dimethylaniline (9·0 g.), aqueous formaldehyde (40%; 1·3 c.c.), and hydrochloric acid (0·2 c.c.) were stirred at 20° for 12 hr., 40° for 24 hr., then 100° for 6 hr., and the product was crystallised from ethanol (180 c.c.), giving 4 : 4′-bisdimethylamino-2 : 2′-diiododiphenylmethane (5·0 g.), m. p. 122—123°. Mascarelli, Toschi, and Zambonini (*Atti R. Accad. Lincei*, 1910, **19**, ii, 341) give m. p. 123° for material prepared in low yield from 2 : 2′-diamino-4 : 4′-bisdimethylaminodiphenylmethane. The 2 : 2′-dibromo-compound was prepared in a similar manner from *m*-bromo-*NN*-dimethylaniline.

UNIVERSITY COLLEGE, HULL. [*Received, November 13th*, 1953.]

Diacid Bases. Part II. Curarising Agents. Derivatives of Diphenyl Ether.*

By A. R. BROWN and F. C. COPP.

[Reprint Order No. 4794.]

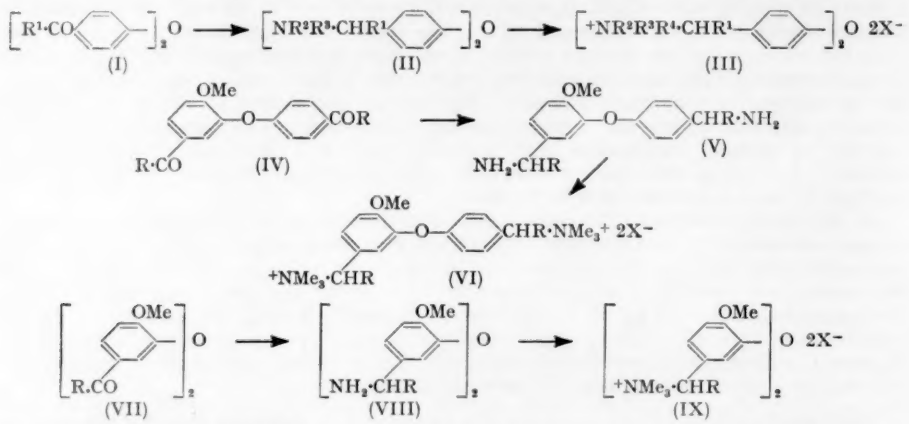
Some diacyldiphenyl ethers have been prepared and, with certain exceptions, converted into the di-(α-aminoalkylphenyl) ethers by (*a*) oximation and reduction, or (*b*) reduction to the dialcohol, followed by bromination and subsequent reaction with the appropriate amine. Aminative reduction was not generally applicable and methods (*a*) and (*b*) also failed in some instances. These diamines were converted into the bisquaternary compounds which had curarising properties (Copp and Mogey, *Nature*, 1950, **165**, 601). Evidence is adduced that the purified bisquaternary salts and the intermediate diamines consisted each of only one stereoisomer.

IN the search for synthetic curarising agents, a large number of bisquaternary compounds, simulating the bisquaternary alkaloid, *dextro*tubocurarine, have already been prepared (see Paton, *J. Pharm. Pharmacol.*, 1949, **1**, 273; Barber, *Annual Rep. Appl. Chem.*, 1949, **34**, 350; Copp, *ibid.*, 1950, **35**, 352; Taylor, *J.*, 1951, 1150; 1952, 142, 1309). Following similar lines of reasoning, we have prepared a number of bisquaternary compounds (III), (VI), and (IX) derived from diphenyl ether. Their relation to *dextro*-tubocurarine, methods of synthesis, and curarising properties of these compounds have already been briefly described (Copp and Mogey, *Nature*, 1950, **165**, 601; see also B.P. 654,433, 654,445) and further chemical details are now reported. The only related known compounds were 4 : 4′-bisaminomethyldiphenyl ether (II; $R^1 = R^2 = R^3 = H$) (Albert, *J.*, 1947, 1452) and 4 : 4′-bis(triethylammonium-methyl)diphenyl ether di-iodide (III; $R^1 = H$, $R^2 = R^3 = R^4 = Et$, X = I) (Funke and Engeler, *Bull. Soc. chim.*, 1950, 340) (cf. Funke and Favre, *ibid.*, 1951, 832).

The starting materials for our salts (III), (VI), and (IX) were the diketones (I), (IV),

* Part I, *J.*, 1953, 3116.

and (VII) respectively. Diketones of this type previously prepared and orientated include (I; R = Me and Ph) (Dilthey, Bach, Grütering, and Hausdörfer, *J. pr. Chem.*, 1927, **117**, 337), (I; R = CH_2Cl) (G.P. 492,321; von Schickh, *Ber.*, 1936, **69**, 242), (IV; R = Me, CH_2Cl), and (VII; R = CH_2Cl) (Tomita, *J. Pharm. Soc. Japan*, 1934, **54**, 167; *ibid.*, 1936, **56**, 99; 1937, **57**, 151; von Schickh, *loc. cit.*) and we have used similar methods for

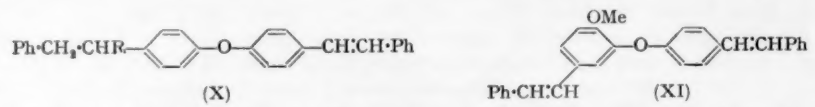


the preparation of a number of analogues of these compounds. The intermediate amines (II), (V), and (VIII) were then obtained by one of the following methods (*a*), (*b*), and (*c*).

(*a*) With the exception of 4 : 4′-di-*o*-toluoyldiphenyl ether, which did not react with hydroxylamine, all the diketones examined in this respect formed well-defined dioximes which were then readily reduced to the diamines (II; $R^2 = R^3 = H$), (V), and (VIII).

(*b*) Reduction by the Meerwein–Ponndorf method was used to convert some of the diketones into the corresponding dialcohols, which were converted into the corresponding dibromides by reaction with hydrogen bromide at −5° (Campbell and Chattaway, *Proc. Roy. Soc.*, 1942, *B*, **130**, 441) and thence into the desired diamines. Usually only these end-products were purified.

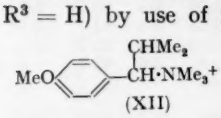
The diketone (I; R = *o*-tolyl) was again unchanged on attempted reduction, which confirms the unreactive nature of its keto-groups. This series of reactions was also apparently unsuitable for the preparation of the amines (II; R = CH_2Ph) and (V; R = CH_2Ph). Thus when (I; R = CH_2Ph) was reduced and the product was brominated and finally treated with alcoholic dimethylamine, a mixture was obtained from which were separated (1) a neutral crystalline product, probably 4-(1-hydroxyphenethyl)-4′-styryldiphenyl ether (X; R = OH), and (2) a crystalline base, probably 4-(1-dimethylaminophenethyl)-4′-styryldiphenyl ether (X; R = NMe_2), characterised as its methiodide and (3) a resinous basic product which contained 4 : 4′-di-(1-dimethylaminophenethyl)diphenyl ether (II; $R^1 = CH_2Ph$, $R^2 = R^3 = Me$) since with methyl iodide it afforded (III; $R^1 = CH_2Ph$, $R^2 = R^3 = R^4 = Me$, X = I) (see also below). The same series of reactions converted 2-methoxy-4′ : 5-bisphenylacetyldiphenyl ether (IV; R = CH_2Ph) into a single neutral crystalline product, probably 2-methoxy-4′ : 5-distyryldiphenyl ether (XI). Analogous observations have recently been made by Goodson and



Christopher (*J. Amer. Chem. Soc.*, 1950, **72**, 358) and Kaye and Parris (*ibid.*, 1952, **74**, 1566) who obtained stilbene as the principal product from 1 : 2-diphenylethyl bromide and piperidine or from 1 : 2-diphenylethyl chloride and 2-aminopyridine and *NN*-dimethyl-*N*′-2-pyridylethylenediamine respectively.

(*c*) Reductive amination (Emerson, "Org. Reactions," Wiley & Sons, 1948, Vol. IV, p. 174) appeared to be of preparative value only for the diamines (II; R = CH_2Ph); the other diketones examined (II; R = Me, Et, and Ph) gave only negligible yields of basic products when reduced in presence of ammonia or a primary or secondary amine. Some instances have been recorded (Emerson, *op. cit.*) where aliphatic aromatic ketones which carry electron-donating groups on the aromatic nucleus, *e.g.*, 4-hydroxypropiophenone, give only low yields of amines under the usual conditions though the isomeric 4-hydroxybenzyl methyl ketone gives an excellent yield of *p*-2-aminopropylphenol when reduced in presence of ammonia.

The diamines (II; $R^2 = R^3 = H$), (V), and (VIII) were most easily converted into the corresponding bistrimethylammonium salts by exhaustive methylation with methyl iodide in presence of sodium carbonate whilst other quaternary salts (III) were prepared as indicated in Table 4 (p. 878). The alternative methylation of (II; $R^1 = Me$, $R^2 = R^3 = H$) by use of formaldehyde and formic acid (Clarke, Gillespie, and Weisshaus, *J. Amer. Chem. Soc.*, 1933, **55**, 4571) led to impure (II; $R^1 = R^2 = R^3 = Me$), which could only be purified as its dipicrate, and it is probable that this methylation was accompanied by decomposition of the type described by Norcross and Openshaw (*J.*, 1949, 1174) and Raison (*ibid.*, p. 2070). The former authors observed that 4-methoxyaralkyltrimethylammonium iodides, *e.g.*, (XII), eliminated trimethylamine hydriodide when heated, and similar fission occurred on attempted methylation of the parent benzylamines with formic acid and formaldehyde. These decompositions appeared to result from spontaneous separation of the charged nitrogen atom under the influence of electron-donation from the methoxyl group and were assisted still further by increased electron-donation (+*I* effect) resulting from lengthening of the side chain. In the present series of compounds, analogous fission presumably results from electron-donation from the (phenyl) ether linkage. Compared with the above methylation of (II; $R^1 = Me$, $R^2 = R^3 = H$), the analogous methylation of (V; R = Me) and (II; $R^1 = Et$, $R^2 = R^3 = H$) gave lower yields of very impure products, evidently the result of enhanced electron-release from the methoxyl group and the lengthened side chain respectively. However, methylation of (II; $R^1 = C_6H_{13}$, $R^2 = R^3 = H$) gave the pure tertiary amine (II; $R^1 = C_6H_{13}$, $R^2 = R^3 = Me$) directly and it is likely that, in this instance, the much longer chain now sterically hindered the nitrogen from escaping; Norcross and Openshaw (*loc. cit.*) observed that 2-*p*-methoxyphenyl-1 : 1-dimethylpiperidinium iodide, in which the quaternary nitrogen is again prevented from escaping, is also stable.



(XII)

Both the final bisquaternary salts and the intermediate diamines may exist in more than one optically inactive form. Since most of these substances were themselves crystalline or gave crystalline derivatives, it seemed probable that only one form of each was present or finally isolated. Further, when the amines (II; $R^1 = CH_2Ph$, $R^2 = R^3 = H$), and ($R^1 = CH_2Ph$, $R^2 = Me$, $R^3 = H$) [which had been prepared by methods (*a*) and (*c*) respectively, see Table 3, p. 877] were exhaustively methylated with methyl iodide, the resulting di-iodides were apparently identical and the same as that prepared from the impure (II; $R^1 = CH_2Ph$, $R^2 = R^3 = Me$) resulting from method (*b*) (see above). This supports the above conclusions since these three di-iodides are unlikely to be identical mixtures of stereoisomers.

Experimental

The physical properties and analytical data of the various intermediate and final products are summarised in Tables 1—4; the preparative methods are generalised or exemplified in the following text.

Diketones (I) (Table 1).—These were prepared by the method of Dilthey *et al.* (*loc. cit.*). Powdered aluminium chloride (108 g.) was covered with carbon disulphide, and the suspension cooled and stirred whilst diphenyl ether (34 g.) was added, followed slowly by propionyl chloride (46 g.). Cooling was continued for 1 hr. and the mixture then heated under reflux for 30 min. after which the supernatant carbon disulphide was decanted and the residue decomposed with ice and hydrochloric acid. The resulting product was dissolved in chloroform, the solution dried and evaporated, and the residue distilled, to give 4 : 4'-*dipropionyldiphenyl ether* (I;

R = Et), b. p. 180—190°/0·1 mm., which rapidly solidified and was recrystallised from methanol.

Diketones (IV) *and* (VII) (Table 1).—These diketones were prepared by using considerably less aluminium chloride, according to Tomita's procedure (*loc. cit.*). A solution of 2 : 2′-di-

TABLE 1. *Diketones* (I), (IV), *and* (VII).

R	B. p.	M. p.	Cryst. from	Yield (%)	Formula	Found (%) C	Found (%) H	Required (%) C	Required (%) H
4 : 4′-Diacyldiphenyl ethers (I).									
Et	180—190°/0·1 mm.	96—97·5°	MeOH	85	$C_{18}H_{18}O_3$	76·65	6·5	76·6	6·4
Pr^n	—	102—103	,,	85	$C_{20}H_{22}O_3$	77·5	6·7	77·4	7·1
Bu^n	—	98—99	EtOH	85	$C_{22}H_{26}O_3$	78·2	7·5	78·1	7·7
n-C_5H_{11}	—	104—105·5	,,	71	$C_{24}H_{30}O_3$	78·6	7·9	78·6	8·2
n-C_6H_{13}	—	102—103	,,	85	$C_{26}H_{34}O_3$	79·2	8·6	79·15	8·7
n-C_7H_{15}	—	103	Pr^{i}OH	63	$C_{28}H_{38}O_3$	79·55	8·9	79·6	9·1
p-C_6H_4Me	—	201—202	BuOH	92	$C_{28}H_{22}O_3$	82·75	5·5	82·7	5·5
o-C_6H_4Me	—	81·4—82·5	MeOH	62	$C_{28}H_{22}O_3$	82·55	5·3	82·7	5·5
Ph·CH_2	—	161—163	AcOH	51	$C_{28}H_{22}O_3$	82·5	5·6	82·7	5·5
2-Methoxy-4′ : 5-bisphenylacetyldiphenyl ether (IV).									
Ph·CH_2	280—300/0·1	134—137	Pr^{i}OH	40	$C_{29}H_{24}O_4$	79·8 (OMe, 6·9)	5·7	79·8 (OMe, 7·1)	5·5
5 : 5′-Diacyl-2 : 2′-dimethoxydiphenyl ethers (VII).									
Me	202—210/0·1	126—128	MeOH	28	$C_{18}H_{18}O_5$	68·8	5·7	68·8	5·8
Ph·CH_2	250—260/10^{-5}	106—107·5	,,	46	$C_{30}H_{26}O_5$	77·6	6·0	77·2	5·6

methoxydiphenyl ether (2·3 g.) and phenylacetyl chloride (3·5 g.) in carbon disulphide (20 ml.) was stirred at 0° whilst powdered aluminium chloride (3·3 g.) was slowly added. The resulting mixture was kept at 0° for 3 hr. and then overnight at room temperature. The product, *2 : 2′-dimethoxy-5 : 5′-bisphenylacetyldiphenyl ether* (VII; R = CH_2Ph), was isolated as in the preceding preparation and distilled (b. p. 240—260°/10^{-5} mm.). The resinous distillate crystallised from ethanol.

Dioximes (Table 2).—A suspension of the diketone, 100% excess of hydroxylamine hydrochloride, and powdered anhydrous sodium carbonate in the appropriate solvent (see Table 2)

TABLE 2. *Dioximes.**

R	M. p.	Cryst. from †	Formula	Found, % N	Required, % N
From (I).					
Et	155—156°	MeOH	$C_{18}H_{20}O_3N_2$	9·1	9·0
Pr^n	122—124	Et_2O–Pet	$C_{20}H_{24}O_3N_2$	8·1	8·2
Bu^n	116—117	,,	$C_{22}H_{28}O_3N_2$	7·5	7·6
n-C_5H_{11}	Two forms, 87—88, 103—104·5	Et_2O–*c*H	$C_{24}H_{32}O_3N_2$	7·2	7·1
n-C_6H_{13}	95—96	Et_2O–Pet	$C_{26}H_{36}O_3N_2$	6·5	6·6
n-C_7H_{15}	76	,,	$C_{28}H_{40}O_3N_2$	6·1	6·2
p-C_6H_4Me	167—169	BuOH	$C_{28}H_{24}O_3N_2$	6·4	6·4
Ph·CH_2	162	EtOH	$C_{28}H_{24}O_3N_2$	6·4	6·4
From (IV).					
Me	166—167·5	Pr^{i}OH	$C_{17}H_{18}O_4N_2$	8·8	8·9
Ph·CH_2	155—156	MeOH	$C_{29}H_{26}O_4N_2$	5·7	6·0
From (VII).					
Me	209—210	Pr^{i}OH	$C_{18}H_{20}O_5N_2$	8·1	8·1
Ph·CH_2	183—184	MeOH–EtOH	$C_{30}H_{28}O_5N_2$	5·5	5·6

* All prepared in Pr^{i}OH, except nos. 5—7 which were prepared in BuOH.
† Pet = light petroleum (b. p. 40—60°), *c*H = *cyclo*hexane.

was heated under reflux for 8 hr. and then poured into water. The resulting dioximes were filtered off and recrystallised.

Diamines (II), (V), *and* (VIII) (Table 3).—(a) *Reduction of dioximes.* 4 : 4′-Diacetyldiphenyl ether dioxime (Dilthey *et al., loc. cit.*) (21·5 g.) was reduced in a saturated solution of ammonia in ethanol (200 ml.) over Raney nickel (2 g.) under hydrogen at 90°/50 atm. (about 3 hr.). The

TABLE 3. *Intermediate diamines* (II), (V), *and* (VIII).

R^1	NR^2R^3	Compound	B. p./mm. or m. p.	Cryst. from	Formula	Found (%) C	H	N	Cl	Required (%) C	H	N	Cl
4 : 4′-*Di*-(1-*dialkylaminoalkyl*)*diphenyl ethers* (II).													
Me	NH_2	Base [a]	152—154°/0·02		$C_{16}H_{20}ON_2$	75·0	7·8	—	—	75·0	7·8	—	—
			39—41°										
		2HCl	266	EtOH–Et_2O	$C_{16}H_{22}ON_2Cl_2$	—	—	8·25	21·3	—	—	8·5	21·6
,,	NMe_2	Base *	154/0·01		$C_{20}H_{28}ON_2$	76·7	8·7	9·2	—	76·9	9·0	9·0	—
		2HCl	248	EtOH–$COMe_2$	$C_{20}H_{30}ON_2Cl_2$	—	—	7·5	18·7	—	—	7·3	18·4
,,	$N<[CH_2]_4>O$	Base [b]	215—220/0·01		$C_{24}H_{32}O_3N_2$	72·8	7·8	7·2	—	72·7	8·1	7·1	—
		$2H_2C_2O_4$ ‡	138—139	MeOH	$C_{28}H_{36}O_{11}N_2$	58·2	6·2	—	—	58·3	6·3	—	—
,,	$N<[CH_2]_4>CH_2$	Base [b]	211/0·01		$C_{26}H_{36}ON_2$	79·4	8·5	7·1	—	79·6	9·2	7·1	—
		$2H_2C_2O_4$ ‡	136—137	EtOH	$C_{30}H_{40}O_9N_2$	62·5	7·0	4·8	—	62·9	7·0	4·9	—
Et	NH_2	Base [a]	176—178/0·07		$C_{18}H_{24}ON_2$	76·35	8·4	9·8	—	76·0	8·5	9·8	—
		2HCl	263	EtOH–EtOAc	$C_{18}H_{26}ON_2Cl_2$	—	—	—	19·8	—	—	—	19·8
Pr^n	,,	Base [a]	173—178/0·05		$C_{20}H_{28}ON_2$	76·7	8·8	9·3	—	76·9	9·0	9·0	—
Bu^n	,,	Base [a]	178—182/0·05		$C_{22}H_{32}ON_2$	—	—	8·1	—	—	—	8·2	—
n-C_5H_{11}	,,	Base [a]	198—200/0·05		$C_{24}H_{36}ON_2$	—	—	7·5	—	—	—	7·6	—
		2HCl	269	MeOH–Et_2O	$C_{24}H_{38}ON_2Cl_2$	—	—	6·45	16·1	—	—	6·35	16·0
,,	$N<[CH_2]_4>CH_2$	Base [b]	235—240/0·05		$C_{34}H_{52}ON_2$	—	—	5·5	—	—	—	5·55	—
n-C_6H_{13}	NH_2	Base [a]	212—218/0·02		$C_{26}H_{40}ON_2$	78·6	9·9	—	—	78·7	10·1	—	—
		2HCl	264—266	Dil. HCl	$C_{26}H_{42}ON_2Cl_2$	—	—	6·0	15·35	—	—	6·0	15·1
,,	NMe_2	Base *	214—216/0·04		$C_{30}H_{48}ON_2$	—	—	6·0	—	—	—	6·2	—
		2HCl	272	EtOH	$C_{30}H_{50}ON_2Cl_2$	—	—	5·2	13·5	—	—	5·3	13·5
n-C_7H_{15}	NH_2	Base [a]	220—230/0·02		$C_{28}H_{44}ON_2$	79·2	10·0	6·7	—	79·2	10·4	6·6	—
		2HCl	261	Dil. HCl	$C_{28}H_{46}ON_2Cl_2$	—	—	—	14·5	—	—	—	14·3
Ph	,,	Base [a]	220—230/0·05		$C_{26}H_{24}ON_2$	—	—	7·05	—	—	—	7·4	—
p-C_6H_4·Me	,,	Base [a]	230—240/0·07		$C_{28}H_{28}ON_2$	—	—	7·0	—	—	—	6·9	—
Ph·CH_2	,,	Base [a]	250—256/0·05		$C_{28}H_{28}ON_2$	82·3	6·9	7·1	—	82·3	6·9	6·9	—
		2Et·SO_3H	255	MeOH–EtOAc	$C_{32}H_{40}O_7N_2S_2$	—	—	4·45	—	—	—	4·4	—
,,	NHMe	Base [c]	266—270/0·05		$C_{30}H_{32}ON_2$	—	—	6·4	—	—	—	6·4	—
4′ : 5-*Bis*-1-*aminoalkyl*-2-*methoxydiphenyl ethers* (V).													
Me	—	Base [a]	174/0·05		$C_{17}H_{22}O_2N_2$	—	—	9·8	—	—	—	9·8	—
			33—35										
		2HCl	196	Pr^iOH–Et_2O	$C_{17}H_{24}O_2N_2Cl_2$	—	—	—	19·5	—	—	—	19·7
Ph·CH_2	—	Base [a]	275—280/10^{-5}		$C_{29}H_{30}O_2N_2$	79·7	6·4	6·2	—	79·4	6·9	6·4	—
5 : 5′-*Bis*-1-*aminoalkyl*-2 : 2′-*dimethoxydiphenyl ethers* (VIII).													
Me	—	Base [a]	190—194/0·05		$C_{18}H_{24}O_3N_2$	68·6	7·6	9·2	—	68·3	7·6	8·85	—
Ph·CH_2	—	Base [a]	†		—	—	—	—	—	—	—	—	—
		$2H_2C_2O_4$ ‡	165	MeOH	$C_{34}H_{36}O_{11}N_2$	63·5	5·35	4·5	—	63·0	5·6	4·3	—

[a, b, c] Prepd. by methods (*a*), (*b*), (*c*) respectively.

* See text for prep. † Decomposed on attempted distillation and not purified. ‡ Di(hydrogen oxalate).

TABLE 4. *Bisquaternary salts* (III), (VI), *and* (IX).

M. p.s accompanied by varying degrees of decomp. All salts were dried at 100° *in vacuo* before analysis; the loss on drying is given where a definite hydrate was apparently present.

	R^1	$NR^2R^3R^4$	X	M. p.	Cryst. from	Formula	Found (%) N	Found (%) X	Found (%) H_2O	Required (%) N	Required (%) X	Required (%) H_2O
(III)	H	NMe_3	I	241—242°	$MeOH–COMe_2$	$C_{20}H_{30}ON_2I_2$	—	45·0	—	—	44·8	—
	Me	,,	,,	218—220	Aq. MeOH	$C_{22}H_{34}ON_2I_2$	4·5	41·8	—	4·7	42·6	—
	,,	NMe_2Et	,,	171—172	Aq. $COMe_2$	$C_{24}H_{38}ON_2I_2$	4·4	40·2	—	4·5	40·7	—
	,,	$MeN<[CH_2]_4>CH_2$	,,	170 (soft. 110)	Aq. PrOH	$C_{28}H_{42}ON_2I_2,5H_2O$	4·3	37·8	11·5	4·1	37·5	11·7
	,,	$MeN<[CH_2]_4>O$	,,	155	Amorphous	$C_{26}H_{38}O_2N_2I_2$	—	36·9	—	—	37·3	—
	,,	$NMe_2·CH_2·Ph$	Br	50—51	Warm H_2O	$C_{34}H_{42}ON_2Br_2$	3·9	25·3	—	4·2	24·3	—
	Et	NMe_3	I	238—240	MeOH	$C_{24}H_{38}ON_2I_2$	4·3	40·8	—	4·5	40·7	—
	Pr^n	,,	,,	241 (soft. 235)	,,	$C_{26}H_{42}ON_2I_2$	4·4	—	—	4·3	—	—
	Bu^n	,,	,,	226 (soft. 222)	EtOH	$C_{28}H_{46}ON_2I_2$	4·4	37·5	—	4·1	37·3	—
	n-C_5H_{11}	,,	,,	Two stages 229—230 248—250	MeOH	$C_{30}H_{50}ON_2I_2$	(C, 50·8; H, 6·8.)			(C, 50·9; H, 7·0.)		
	,,	,,	Br	208—209	$EtOH–Et_2O$	$C_{30}H_{50}ON_2Br_2,H_2O$	—	26·4	3·0	—	26·0	2·8
	,,	$MeN<[CH_2]_4>CH_2$	I	133	Pr^iOH	$C_{36}H_{58}ON_2I_2$	—	31·9	—	—	32·2	—
	,,	,,	Br	69—72 (deliquesc.)	$Pr^iOH–Et_2O$	$C_{36}H_{58}ON_2Br_2,2H_2O$	—	23·4	5·0	—	23·0	4·9
	n-C_6H_{13}	NMe_3	I	Two stages 228—229 247—249	Insol.	$C_{32}H_{54}ON_2I_2$	—	34·7	—	—	34·5	—
	,,	,,	Cl	80—85	Resin	$C_{32}H_{54}ON_2Cl_2$	—	12·9	—	—	12·8	—
	n-C_7H_{15}	,,	I	Two stages 220—221 240—242	EtOH	$C_{34}H_{58}ON_2I_2$	—	33·3	—	—	33·2	—
	,,	,,	Br	211	$EtOH–Et_2O$	$C_{34}H_{58}ON_2Br_2$	—	23·6	—	—	23·8	—
	Ph	,,	Cl *	166—167	Aq. $COMe_2$	$C_{32}H_{38}ON_2Cl_2,4H_2O$	4·9	13·1	11·5	5·2	13·2	11·8
	p-C_6H_4Me	,,	,, *	135—136	$EtOH–Et_2O$	$C_{34}H_{42}ON_2Cl_2,4H_2O$	4·7	12·6	10·8	5·0	12·5	11·3
	$Ph·CH_2$	,,	I	Two stages 210—212 266—267	MeOH	$C_{34}H_{42}ON_2I_2$	—	33·6	—	—	33·9	—
	,,	,,	Br	267—268 (soft. 214—216)	Aq. $COMe_2$	$C_{34}H_{42}ON_2Br_2$	—	24·4	—	—	24·5	—
(VI)	Me	—	I	186—187	,,	$C_{23}H_{36}O_2N_2I_2$	4·3	40·9	—	4·5	40·6	—
	$Ph·CH_2$	—	Br *	170	Amorphous	$C_{35}H_{44}O_2N_2Br_2,2H_2O$	—	23·3	5·0	—	23·4	5·0
(IX)	Me	—	I	172—173	Aq. $COMe_2$	$C_{24}H_{38}O_2N_2I_2$	4·3	38·8	—	4·3	38·7	—
	$Ph·CH_2$	—	,,	171—172	Amorphous	$C_{36}H_{46}O_2N_2I_2$	3·3	31·6	—	3·5	31·4	—

* Prepared directly from the crude iodides which were not investigated.

catalyst was then filtered off, the filtrate evaporated under reduced pressure, and the residue distributed between ether and N-hydrochloric acid. The acid layer was made alkaline with concentrated aqueous sodium hydroxide, and the precipitated oil extracted with ethyl acetate since it was immiscible with ether. The solution was dried and evaporated, and the residual 4 : 4′-*bis*-1″-*aminoethyldiphenyl ether* (II; R^1 = Me, R^2 = R^3 = H), distilled *in vacuo* (b. p. 152—154°/0·02 mm.; 15 g.).

(b) *Meerwein–Ponndorf reduction, etc.* 4 : 4′-Diacetyldiphenyl ether (I; R = Me) (20 g.) was reduced with aluminium *iso*propoxide (25 g.) in dry *iso*propanol (250 ml.) (Wilds, " Organic Reactions," Wiley & Sons, 1944, Vol. II, p. 199). When reduction was complete the mixture was poured into excess of dilute hydrochloric acid, and the precipitated 4 : 4′-*bis*-1″-*hydroxyethyldiphenyl ether* (see below) was separated at the centrifuge. It was then dissolved in a mixture of ether and toluene, and the solution dried overnight (Na_2SO_4), filtered, and saturated at −5° with hydrogen bromide during 3 hr. The red mixture was poured on ice, and the organic layer separated, washed with aqueous sodium carbonate, dried for 10 min. (Na_2SO_4), and filtered. Morpholine (40 ml.) was added to the filtrate, and the mixture heated on a steam-bath. After 3 hr., the resulting suspension was cooled and filtered, and the filtrate exhaustively extracted with 0·5N-hydrochloric acid. The regenerated base was collected in ether and distilled *in vacuo*, and the fraction, b. p. 220—230°/0·01 mm. (11·5 g.), was added to a solution of oxalic acid (6 g.) in ethanol. Addition of ether gave a gum from which the supernatant liquors were decanted. The residue was stirred with acetone, the acetone decanted, and the residue redissolved in methanol. 4 : 4′-*Bis*-1″-*morpholinoethyldiphenyl ether di*(*hydrogen oxalate*) slowly crystallised in needles, m. p. 138—139° (14·1 g.). The regenerated *base* had b. p. 216—217°/0·01 mm.

Another preparation of the intermediate, 4 : 4′-bis-1″-hydroxyethyldiphenyl ether slowly solidified and, recrystallised from ether–toluene, had m. p. 86—87° (Found: C, 74·5; H, 7·3. $C_{16}H_{18}O_3$ requires C, 74·4; H, 7·0%). 4′ : 5-*Di*-(1-*hydroxy*-2-*phenylethyl*)-2-*methoxydiphenyl ether* (see below), similarly prepared, slowly crystallised from toluene and had m. p. 82—83° (Found: C, 78·6; H, 6·2. $C_{29}H_{28}O_4$ requires C, 79·1; H, 6·4%), but 4 : 4′-bis-1″-hydroxyhexyldiphenyl ether and 4 : 4′-di-(1-hydroxyphenethyl)diphenyl ether (see below) could not be crystallised. They decomposed on attempted distillation.

(c) *Reductive amination.* 4 : 4′-Bisphenylacetyldiphenyl ether (I; R = CH_2Ph) (11 g.) was reduced in a saturated solution of methylamine in *n*-butanol (200 ml.) over Raney nickel (3 g.) under hydrogen at 80°/90 atm. The resulting 4 : 4′-*di*-(1-*methylaminophenethyl*)*diphenyl ether* (II; R^1 = CH_2·Ph, R^2 = H, R^3 = Me) was separated from non-basic products as before; it was a viscid liquid (4·2 g.), b. p. 266—270°/0·01 mm.

Bisquaternary Compounds (III), (VI), *and* (IX) (Table 4).—A solution of 4 : 4′-bis-1″-aminoethyldiphenyl ether (4·6 g.) and methyl iodide (20 ml.) in methanol (50 ml.) was heated to reflux with anhydrous sodium carbonate (4·2 g.). After 2 hr., the inorganic material was filtered off and the filtrate cooled, 4 : 4′-*di*-(1-*trimethylammoniumethyl*)*diphenyl ether di-iodide* (III; R^1 = R^2 = R^3 = R^4 = Me, X = I) separating in thick prisms, m. p. 218—219° (decomp.). Alternatively, a small excess of methyl iodide was added to methanolic 4 : 4′-bis-1″-dimethylaminoethyldiphenyl ether (II; R^1 = R^2 = R^3 = Me) (see below); there was a vigorous reaction and the desired di-iodide rapidly crystallised, having m. p. 218—219° undepressed on admixture with the di-iodide obtained as above. The quaternisations of other ditertiary amines prepared by method (*b*) were similarly effected.

The di-iodides of the higher members of the series were too insoluble in water for biological testing and were therefore converted into the more soluble dichlorides or dibromides by treatment with the appropriate silver halide in boiling methanol.

4 : 4′-*Bis*-1″-*dimethylaminoethyldiphenyl Ether* (II; R^1 = R^2 = R^3 = Me) (Table 3).—4 : 4′-Bis-1″-aminoethyldiphenyl ether (28 g.) was methylated with formic acid (60 ml.) and aqueous formaldehyde (37%; 48 ml.) (see Clarke, Gillespie, and Weisshaus, *loc. cit.*). After 10 hours' heating at 100°, concentrated hydrochloric acid (8 ml.) was added before evaporation *in vacuo*. Excess of concentrated aqueous ammonia was added to the residue, the separated oil taken up into ethyl acetate, and the residual aqueous layer extracted several times with the same solvent. The combined extracts were dried and evaporated, and the residue distilled, but the product (12·3 g.) was impure. It was therefore treated with excess of picric acid in ethanol, and the resulting dipicrate recrystallised from acetic acid from which it separated in yellow prisms, m. p. 200°. This was decomposed by addition to a warm solution of concentrated hydrochloric acid in acetic acid, the solution quickly cooled, and the precipitated picric acid filtered off. The filtrate was poured into water, a further crop of picric acid removed, and the solution

extracted several times with ether. The residual aqueous solution was made strongly alkaline with concentrated aqueous sodium hydroxide and then extracted repeatedly with ethyl acetate. The combined extracts were dried and evaporated; the residual *product* (II; $R^1 = R^2 = R^3 =$ Me) had b. p. 153—158°/0·01 mm.

4 : 4′-*Bis*-1″-*dimethylaminoheptyldiphenyl ether* (II; $R^1 = C_6H_{13}$, $R^2 = R^3 =$ Me) was analogously prepared but purification *via* the dipicrate was unnecessary. It was an oil, b. p. 212—217°/0·04 mm.

Reduction, etc., of 4 : 4′-*Bisphenylacetyldiphenyl Ether* (I; R = CH_2Ph). *Attempted Preparation of* 4 : 4′-*Di*-(1-*dimethylaminophenethyl*)*diphenyl Ether* (II; $R^1 = CH_2Ph$, $R^2 = R^3 =$ Me).—4 : 4′-Bisphenylacetyldiphenyl ether (7·5 g.) was reduced with aluminium *iso*propoxide (12 g.) in *iso*propanol (200 ml.), the resulting dialcohol brominated as previously described, and the resulting dibromide and alcoholic dimethylamine (20%; 100 ml.) caused to react in an autoclave at 90°. After 3 hr. the mixture was cooled, the ethanol evaporated, and water added to the residue. The insoluble material was collected in ether, and the basic products (A) were separated from the neutral products (B) with 0·5N-hydrochloric acid.

Fraction (A) was a resin (3·7 g.), b. p. 230—240°/0·1 mm. Its solution in methanol rapidly deposited crystals of 4-(1-*dimethylaminophenethyl*)-4′-*styryldiphenyl ether* (X; R = NMe_2) (1·9 g.), m. p. 111—112° (from *iso*propanol) (Found: C, 85·6; H, 6·9; N, 3·4. $C_{30}H_{29}ON$ requires C, 85·9; H, 7·0; N, 3·3%). Its *methiodide*, crystallised from aqueous ethanol, had m. p. 158° (Found: N, 2·4; I, 22·5. $C_{31}H_{32}ONI$ requires N, 2·4; I, 22·6%). Evaporation of the original methanolic mother-liquors of this base gave a gum, b. p. 228—235°/0·01 mm. (1·4 g.). With methyl iodide in methanol, it gave a crystalline solid (1·1 g.), m. p. 260—267° after shrinking at 200—205°. This was twice recrystallised from methanol–ethanol, yielding slender prisms of 4 : 4′-di-(2-phenyl-1-trimethylammonium-ethyl)diphenyl ether di-iodide (III; $R^1 = CH_2Ph$, $R^2 = R^3 = R^4 =$ Me, X = I) (Table 4; see below).

Evaporation of the ethereal solution of (B) gave a crystalline residue of 4-(1-*hydroxyphenethyl*)-4′-*styryldiphenyl ether*; crystallised from *iso*propanol, this had m. p. 113—114° (Found: C, 85·6; H, 6·5. $C_{28}H_{24}O_2$ requires C, 85·7; H, 6·2%).

When 2-methoxy-4′ : 5-bisphenylacetyldiphenyl ether (IV; R = CH_2Ph) was subjected to the same series of reactions, only 2-*methoxy*-4′ : 5-*distyryldiphenyl ether* (XI), m. p. 177° (from ethyl acetate), resulted (Found: C, 86·2; H, 5·7. $C_{29}H_{24}O_2$ requires C, 86·1; H, 5·9%).

4 : 4′-*Di*-(2-*phenyl*-1-*trimethylammoniumethyl*)*diphenyl Ether Di-iodide* (III; $R^1 = CH_2Ph$, $R^2 = R^3 = R^4 =$ Me, X = I).—Exhaustive methylation of 4 : 4′-di-(1-aminophenethyl)diphenyl ether (II; $R^1 = CH_2Ph$, $R^2 = R^3 =$ H), prepared by method (*a*) (see Table 3), gave the above *di-iodide*, m. p. 266—267° after sintering at 210—212° (from methanol) (Found: I, 33·6. $C_{34}H_{42}ON_2I_2$ requires I, 33·9%). Similar methylation of 4 : 4′-di-(1-methylaminophenethyl)diphenyl ether, prepared by method (*c*) (see above and Table 3), gave a product, m. p. 265—266°, sintering at 214—215° (Found: N, 3·5; I, 33·5. Calc. for $C_{34}H_{42}ON_2I_2$: N, 3·5; I, 33·9%). The m. p.s of these two products showed no depression on admixture with each other or on admixture with the (same) di-iodide obtained from the impure 4 : 4′-bis-(1-dimethylaminophenethyl)diphenyl ether (II; $R^1 = CH_2$·Ph, $R^2 = R^3 =$ Me), prepared by method (*b*) (see above).

We are indebted to Mr. A. Bennett and Mr. P. R. W. Baker of this Division for the microanalyses and to Professor A. Albert, of the Australian National University, Euston Road, London, N.W.1, for a gift of 4 : 4′-aminomethyldiphenyl ether.

THE CHEMICAL DIVISION, THE WELLCOME RESEARCH LABORATORIES,
BECKENHAM, KENT. [*Received, November 13th*, 1953.]

Organometallic and Organometalloidal Compounds. Part VIII. Properties of Trifluoromethyl-arsenic Acids and of Other Fluorine-containing Acids.*

By H. J. Emeléus, R. N. Haszeldine, and Ram Chand Paul.

[Reprint Order No. 4628.]

Trifluoromethylarsonic acid, readily obtained by oxidative hydrolysis of di-iodo(trifluoromethyl)arsine, is readily converted into the pyro-acid, and into the anhydride $CF_3 \cdot AsO_2$. Trifluoromethylarsonic acid and bistrifluoromethylarsinic acid are almost completely ionised in aqueous solution, and are thus much stronger acids than methylarsonic acid or cacodylic acid. The order of decreasing strength of a series of acids in anhydrous acetic acid is $H_2SO_4 > HCl > (CF_3)_2AsO \cdot OH > CF_3 \cdot AsO(OH)_2 \gg CF_3 \cdot CO_2H$, HNO_3, $C_3F_7 \cdot CO_2H$. Trifluoroacetic acid is slightly stronger than heptafluorobutyric acid.

The preparation of bistrifluoromethylarsinic acid $(CF_3)_2AsO \cdot OH$ by oxidative hydrolysis of iodobistrifluoromethylarsine was described in Part VI (Emeléus, Haszeldine, and Walaschewski, *J.*, **1953**, 1552), and this acid was shown to be much stronger than the unsubstituted cacodylic acid. In the present investigation trifluoromethylarsonic acid $CF_3 \cdot AsO(OH)_2$ has been prepared, and its conductivity compared with that of bistrifluoromethylarsinic acid in water, and with mineral acids, the fluoroarsinic acid, and trifluoroacetic and heptafluorobutyric acids in acetic acid solution.

Di-iodo(trifluoromethyl)arsine is stable to water, but when treated with aqueous hydrogen peroxide undergoes exothermic oxidative hydrolysis to iodine and trifluoromethylarsonic acid:

$$CF_3I \xrightarrow{As} CF_3 \cdot AsI_2 \xrightarrow[-H_2O]{H_2O_2} CF_3 \cdot AsO(OH)_2$$

This is a stable white solid which resembles arsenic acid in that it undergoes progressive dehydration *in vacuo* forming first a pyro-acid and then an anhydride:

$$CF_3 \cdot AsO(OH)_2 \xrightarrow{35°/10^{-3}\ mm.} CF_3 \cdot As\begin{matrix} O \\ \| \\ OH \end{matrix} \!\!-\!\! O \!\!-\!\! \begin{matrix} O \\ \| \\ HO \end{matrix} As \cdot CF_3 \xrightarrow{73°/10^{-3}\ mm.} CF_3 \cdot AsO_2$$

The ortho-acid is characterised by its infra-red spectrum (Table 1) which reveals the As·OH group, and by its mono- and di-silver salts. The monosilver salt, shown to contain the As·OH group by its infra-red spectrum (Table 1), is readily soluble in water; the disilver salt shows no As·OH group vibrations in the infra-red (Table 1), and has a much lower solubility.

Table 1. *Infra-red spectra* (in $\mu\mu$).

Compound	C.S. No.*	As·O–H	C–F	As=O	CF_3 deformation
$CF_3 \cdot AsO(OH)_2$	97	4·3	8·67	12·33	13·50
$(CF_3)_2AsO \cdot OH$	34	4·3	8·44	12·27	13·54
$CF_3 \cdot AsO(OH)(OAg)$	94	4·3	8·69	12·17	13·67
$CF_3 \cdot AsO(OAg)_2$	95	Absent	8·53 8·75	12·05	13·41
$(CF_3)_2AsO(OAg)$	35	Absent	8·77	12·13(?)	13·56
$[CF_3 \cdot AsO(OH)]_2O$	92	4·35	8·42 8·70	12·35	13·40
$CF_3 \cdot AsO_2$	96	Absent	8·83	12·25	13·64

* Spectra thus marked have been deposited with the Society. Photocopies can be obtained (price 3*s.* 0*d.* per copy per spectrum, post free) on application to the General Secretary stating the C.S. No.

The pyro-acid, which shows the As·O–H vibration in the infra-red (Table 1), reverts to the ortho-form in water, and attempts to prepare its silver salt were unsuccessful; monosilver trifluoromethylarsonate was not converted into the disilver salt of the pyro-acid when heated *in vacuo*.

* Part VII, Bennett, Emeléus, and Haszeldine, *J.*, 1953, 1565.

The anhydride, $CF_3 \cdot AsO_2$, shows no As·O–H absorption in the infra-red (Table 1), and is immediately converted into the ortho-acid when dissolved in water. Bistrifluoromethylarsinic acid does not form an anhydride quantitatively when heated *in vacuo*, and intramolecular dehydration clearly occurs more readily than intermolecular dehydration in these arsenic acids. Methylarsonic acid forms a pyro-acid, but further dehydration to the anhydride has not been reported.

Attempts to prepare tristrifluoromethylarsine oxide, the anhydride of the hypothetical acid $(CF_3)_3As(OH)_2$, the acid itself, or its ethyl ester, by the following reactions were unsuccessful:

$$(CF_3)_3AsCl_2 \xrightarrow{H_2O} (CF_3)_3As(OH)_2 \longrightarrow (CF_3)_3AsO$$

$$(CF_3)_3AsCl_2 \xrightarrow[H_2O]{Ag_2O} (CF_3)_3As(OH)_2$$

$$(CF_3)_3AsCl_2 \xrightarrow{CH_3 \cdot CO_2H} CH_3 \cdot COCl + (CF_3)_3AsO + HCl$$

$$(CF_3)_3AsCl_2 \xrightarrow{EtOH} (CF_3)_3As(OEt)_2 + 2HCl$$

The reaction with water gave tristrifluoromethylarsine (mainly) and bistrifluoromethylarsinic acid; with silver oxide, chlorobistrifluoromethylarsine, carbon dioxide, fluoride, and bistrifluoromethylarsinic acid were obtained, *i.e.*, one trifluoromethyl group was broken down to carbonate and fluoride. Acetic acid gave mainly chlorobistrifluoromethylarsine and chlorotrifluoromethane, which are the usual thermal breakdown products of tristrifluoromethylarsenic dichloride. Ethanol converted the last compound into tristrifluoromethylarsine quantitatively.

Two reactions were studied in unsuccessful attempts to prepare methyltrifluoromethylarsinic acid, required for comparison with bistrifluoromethylarsinic acid:

$$(CF_3)_2AsMe \xrightarrow{I_2} (CF_3)(Me)AsI \xrightarrow{H_2O_2} (CF_3)(Me)AsO \cdot OH$$

$$CF_3 \cdot AsI_2 \xrightarrow{MeMgI} CF_3AsMe_2 + (CF_3)(Me)AsI \qquad (\uparrow H_2O_2)$$

During the preparation of methylbistrifluoromethylarsine from tristrifluoromethylarsine by the exchange reaction with methyl iodide described in Part VI (*loc. cit.*), it was noted that the last two compounds appear to form a 1 : 1 azeotrope; this is probably a weakly-bonded molecular compound, which is the nearest approach to salt formation that has yet been observed with tristrifluoromethylarsine (see *J.*, 1952, 2552; 1953, 1552). The reaction of methylbistrifluoromethylarsine with iodine yielded only methyl iodide, trifluoroiodomethane, and complex products.

The replacement of only one iodine atom in di-iodo(trifluoromethyl)arsine by methyl could not be achieved. Dimethyltrifluoromethylarsine was isolated, however, and thus completes the series $(CF_3)_3As$ (b. p. 33°), $(CF_3)_2AsMe$ (b. p. 52°), $CF_3 \cdot AsMe_2$ (b. p. 58°), and $AsMe_3$ (b. p. 49·5°). The highest boiling point is reached when only a few fluorine atoms are present in the molecule, an effect often noted with other fluorine compounds.

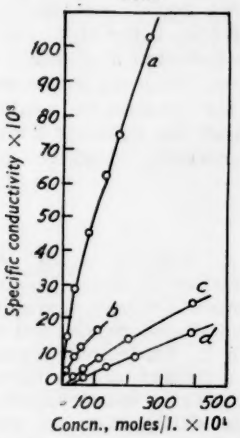
Tristrifluoromethylarsine reacts rapidly with aqueous sodium hydroxide (Brandt, Emeléus, and Haszeldine, *J.*, 1952, 2552), methylbistrifluoromethylarsine reacts much more slowly (Part VI, *loc. cit.*), and trimethylarsine is stable. Dimethyltrifluoromethylarsine has now been found to fit into this sequence; fluoroform is produced quantitatively (*i.e.*, without liberation of fluoride), but extremely slowly, even when the arsine is heated with strong aqueous base for several days.

Trifluoromethylarsonic acid and bistrifluoromethylarsinic acid are almost completely ionised in water (Table 2), and are thus much stronger acids than methylarsonic acid ($K_1 = 2{\cdot}46 \times 10^{-4}$, $K_2 = 5{\cdot}69 \times 10^{-9}$; Backer and Bolt, *Rec. Trav. chim.*, 1935, **54**, 186), phenylarsonic acid ($K_1 = 3{\cdot}4 \times 10^{-4}$; $K_2 = 3{\cdot}3 \times 10^{-9}$; Pressman and Brown, *J. Amer. Chem. Soc.*, 1943, **65**, 540), or arsenic acid [$K_1 = 5 \times 10^{-3}$, $K_2 = 4 \times 10^{-5}$, $K_3 = 6 \times 10^{-10}$ (20°); Rosenheim and Antelmann, *Z. anorg. Chem.*, 1930, **187**, 385; **193**, 73. Washburn and

Strachan (*J. Amer. Chem. Soc.*, **1913**, **35**, 681) report $4{\cdot}3 \times 10^{-3}$ for K_1 at 25°]. Cacodylic acid is amphoteric ($K_a = 7{\cdot}5 \times 10^{-7}$, $K_b = 5{\cdot}6 \times 10^{-13}$; Fraenkel, *Z. physikal. Chem.*, 1907, **60**, 202; Holmberg, *ibid.*, 1910, **70**, 153) and is not much stronger than carbonic acid ($K_1 = 3{\cdot}2 \times 10^{-7}$) or hydrogen sulphide ($K_1 = 1{\cdot}3 \times 10^{-7}$).

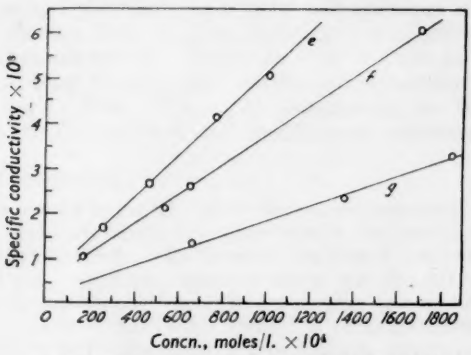
Equivalent conductivities of the acids $CF_3{\cdot}AsO(OH)_2$ and $(CF_3)_2AsO{\cdot}OH$ at infinite dilution have been extrapolated from the plot of the λ–$\sqrt{c}$ data summarised in Tables 3 and 4; the values are **398·0** and **399·5**, respectively. The trifluoromethylarsonic acid behaves as a monobasic acid, since, for a dibasic acid with both hydrogen atoms ionised, a much higher value for the equivalent conductivity would be expected. At dilutions greater than 0·001M, however, the experimental points on the graph of the data in Table 3 lie above the straight line drawn through the points at higher concentrations. This fact has been

FIG. 1. *Conductivities in acetic acid.*



(*a*) H_2SO_4. (*c*) $(CF_3)_2AsO{\cdot}OH$
(*b*) HCl (*d*) $CF_3{\cdot}AsO(OH)_2$

FIG. 2. *Conductivities in acetic acid.*



(*e*) $CF_3{\cdot}CO_2H$. (*f*) HNO_3. (*g*) $C_3F_7{\cdot}CO_2H$.

repeatedly verified and probably represents a slight ionisation of the second hydrogen atom at these high dilutions. By contrast, methylarsonic acid is dibasic (see above). The degree of ionisation (α) of trifluoromethylarsonic and bistrifluoromethylarsinic acids in aqueous solution as a function of concentration is shown in Table 2.

TABLE 2.

		$CF_3{\cdot}AsO(OH)_2$			$(CF_3)_2AsO{\cdot}OH$		
c	$\sqrt{c}$	λ_c	λ_x	α	λ_c	λ_x	α
0·05	0·2236	328·4	365·9	0·897	294·0	369·3	0·796
0·01	0·1000	366·8	383·2	0·957	352·8	385·0	0·916
0·002	0·0447	384·0	391·3	0·981	379·0	392·8	0·964
0·001	0·0316	388·2	393·2	0·987	384·9	394·8	0·975

(See p. 885 for meaning of c, λ_c, and λ_x.)

Since these trifluoromethyl acids are highly ionised, measurements in aqueous solution are not suitable for comparison of their relative strengths or for comparison with other acids which are strong in aqueous solution. Measurements on nitric, hydrochloric, hydrobromic, perchloric, and sulphuric acids in anhydrous acetic acid, made by Kolthoff and Willman (*J. Amer. Chem. Soc.*, 1934, **56**, 1007) and Hlasko and Michalski (*Roczn. Chem.*, 1938, **18**, 220), show that in this solvent the relative strengths of the acids are well differentiated and may be placed in the order $HNO_3 < HCl < H_2SO_4 < HBr < HClO_4$. The conductivities of the trifluoromethyl arsenic acids and of trifluoroacetic and heptafluorobutyric acids have now been measured in anhydrous acetic acid to enable a general comparison of acid strength to be

made. The results (Table 5) are best represented graphically as in the Figures, where recorded data on sulphuric, hydrochloric, and nitric acid (Kolthoff and Willman, *loc. cit.*) are also shown. The conductivities are much lower in acetic acid (dielectric constant 6 at 25°) than in aqueous solution. It is seen that bistrifluoromethylarsinic acid is stronger than trifluoromethylarsonic acid in anhydrous acetic acid, although it is slightly less ionised in aqueous solution. The increase in acidity can be attributed to the presence of two electron-attracting trifluoromethyl groups [cf. C_3F_7·CHMe·OH, $K = 4 \times 10^{-12}$; $(C_3F_7)_2$CH·OH, $K = 30 \times 10^{-12}$; Haszeldine, *J.*, 1953, 1757].

Swarts (*Bull. Acad. roy. Belg.*, 1922, **8**, 343) showed that trifluoroacetic acid in aqueous solution was almost completely ionised, and this acid has often been loosely called as strong as hydrochloric acid. The Figures show that the fluoro-carboxylic acids are relatively weak in acetic acid, and are comparable only with nitric acid. Trifluoroacetic acid is slightly stronger than heptafluorobutyric acid, and a reason for this has been suggested (*J.*, 1953, 1758). The order of acid strength in anhydrous acetic acid is thus $H_2SO_4 > HCl > (CF_3)_2AsO{\cdot}OH > CF_3{\cdot}AsO(OH)_2 \gg CF_3{\cdot}CO_2H$, HNO_3, $C_3F_7{\cdot}CO_2H$. It is thus apparent that when a polyfluoroalkyl group such as trifluoromethyl is attached to carbon, as in a carboxylic acid, the acid is much weaker than when the group is attached to an element such as arsenic. It has similarly been shown that in aqueous solution trifluoromethylphosphonic acid is (apart from pyrophosphoric acid) the strongest known acid of phosphorus ($K_1 = 6{\cdot}8 \times 10^{-2}$, $K_2 = 1{\cdot}2 \times 10^{-4}$; Bennett, Emeléus, and Haszeldine, Amer. Chem. Soc. Meeting, Chicago, Sept. 1953).

Experimental

Trifluoromethylarsonic Acid.—Di-iodotrifluoromethylarsine (4·0 g.; Part VI, *loc. cit.*) was condensed into a previously evacuated tube which contained unstabilised hydrogen peroxide (100-vol.; 3 ml.) and water (5 ml.). An exothermic reaction occurred at room temperature, and the tube was cooled intermittently in ice. The iodine was filtered off after 20 min., and the solution was evaporated *in vacuo* over phosphoric anhydride (12 hr.). Transparent crystals corresponding to a hydrate containing 7—8 mols. of water first separated, and on further evaporation changed to a white powder (1·85 g., 96%). The solid gave no test for iodide or iodate. For analysis the *trifluoromethylarsonic acid* [Found: CF_3(as CHF_3), 37·2; As, 40·1. $CH_2O_3F_3As$ requires CF_3, 35·6; As, 38·6%] was dried for 4 hr. at 10^{-2} mm., then a sample (0·1470 g.) was heated at 80° for 24 hr. with 15% aqueous sodium hydroxide (15 ml.); the fluoroform evolved was measured, and arsenic was determined in the residual solution by precipitation of silver arsenate and volumetric estimation of the silver by Pearce's method as improved by Waddell (*Ind. Eng. Chem.*, 1919, **11**, 939). The discrepancy in the analytical data is attributed to partial pyro-acid formation (see below).

Trifluoromethylarsonic acid (0·1021 g.) was dissolved in water (55·2 ml.) to give an approx. 0·01M-solution, which had pH 2·10. Titration of this solution (10 ml.) with 0·1N-sodium hydroxide gave a first point of inflection at pH 3·77, from which the equivalent weight of the acid is 93·3 [$CF_3{\cdot}AsO(OH)(ONa)$ requires equiv., 96·95]. Rapid titration gave a second point of inflection at pH 8·2; when the solution was left at this pH, decomposition occurred, with evolution of fluoroform, and the pH decreased.

A second sample of the acid, stored in a bottle for 3 months, had an equivalent weight of 96·8, indicating conversion of pyro- into ortho-acid.

Silver Salts.—Trifluoromethylarsonic acid (2·0 g.), dissolved in water (10 ml.), was treated with alkali-free silver oxide (1·3 g., 10% excess for the mono-silver salt) at 60°. The solution was filtered and evaporated *in vacuo* over phosphoric anhydride to give a pale brown first crop of crystals (see below) followed by a white main crop of the *monosilver* salt (1·3 g., 40%) [Found: CF_3(as CHF_3), 22·6; As, 24·6; Ag, 35·7. CHO_3F_3AsAg requires CF_3, 22·9; As, 24·9; Ag, 35·9%].

The first crop of solid was combined with a further quantity of the monosilver salt (1·5 g.) obtained from the mother-liquor, and dissolved in water (20 ml.). Treatment with an excess of silver oxide (1·0 g.) at 60° for 15 min. gave, by filtration and evaporation *in vacuo*, the *disilver* salt (0·5 g., 30%) which was recrystallised from water [Found: CF_3(as CHF_3), 16·7; As, 18·5; Ag, 52·7. $CO_3F_3AsAg_2$ requires CF_3, 16·9; As, 18·4; Ag, 52·9%].

Pyrotrifluoromethylarsonic Acid.—A sample of trifluoromethylarsonic acid (1·00 g.), which had been partly converted into the pyro-acid by drying *in vacuo* over phosphoric anhydride for

4 hr., was heated at 33° for 12 hr. *in vacuo*. There was no further loss in weight after a further 4 hr.' heating under the same conditions. The loss in weight (0·011 g.) showed that the starting product contained 23% of ortho- and 77% of pyro-acid. The *trifluoromethylpyroarsonic acid* (Found: CF_3, 37·2; As, 40·9. $C_2H_3O_5F_3As_2$ requires CF_3, 37·3; As, 40·6%) was titrated potentiometrically with 0·1N-sodium hydroxide (Found: equiv., 92·75. $C_2H_3O_5F_3As_2$ requires equiv., 92·5), thus showing complete conversion of the pyro- into the ortho-acid in water.

The pyro-acid (0·4 g.) was dissolved in water (10 ml.) and heated with silver oxide (0·27 g.) for 15 min. at 50° in an attempt to prepare a silver salt of the pyro-acid. The middle crop of crystals was shown by analysis and infra-red spectroscopic examination to be the monosilver salt of trifluoromethyl(ortho)arsonic acid (Found: CF_3, 23·0; As, 24·4; Ag, 35·8. Calc. for CHO_3F_3AsAg: CF_3, 22·9; As, 24·9; Ag, 35·9%). A sample of the monosilver salt was unchanged in weight, and its infra-red spectrum was unaltered after 48 hr.' heating at $100°/10^{-2}$ mm.

Trifluoromethylarsonic Anhydride.—The pyro-acid (0·5100 g.), heated at 56° under 10^{-2} mm. for 12 hr., lost 0·0130 g., and there was no further loss in weight after another 6 hr. at this temperature. After the acid had been heated at 73° for 48 hr. the total loss in weight was 0·0253 g. The *trifluoromethylarsonic anhydride* (Found: CF_3, 40·2; As, 42·8. CO_2F_3As requires CF_3, 39·2; As, 42·6%) would theoretically be formed by loss in weight of 0·0250 g. Titration with carbonate-free aqueous sodium hydroxide gave equiv., 88·06 (CO_2F_3As requires equiv., 87·95).

Conductivity Measurements.—Bistrifluoromethylarsinic acid was prepared from iodobistrifluoromethylarsine (*J.*, 1953, 1522). Trifluoroacetic and heptafluorobutyric acid were freshly distilled (b. p. 72·0° and 121°, respectively). "AnalaR" acetic acid, further purified by Kolthoff and Willman's method (*loc. cit.*), had m. p. 16·5° and specific conductivity $1·5—1·8 \times 10^{-8}$. Haszeldine and Woolf's apparatus (*Chem. and Ind.*, 1950, 544) was used to measure conductivity, with cells with constants 13·29 (*A*), 4·359 (*B*), and 0·05338 (*C*). Auxiliary resistances were used in parallel when dilute solutions were being measured. Solutions were prepared by weight and subsequent dilutions were by weight. All measurements were at 25° ± 0·02°.

The results are given in Tables 3 and 4, where c = concentration in moles/l., κ = specific conductivity, λ_c = molecular conductivity, $\lambda_{corr.}$ = corrected molecular conductivity, calculated from the equation $\lambda_c = \lambda_{corr.} - (A + B\lambda_{corr.})\sqrt{c}$ with $A = 60·21$, $B = 0·2289$.

TABLE 3. $CF_3 \cdot AsO(OH)_2$.

10^4c	$10^2\sqrt{c}$	$10^4\kappa$	λ_c	$\lambda_{corr.}$	Cell	10^4c	$10^2\sqrt{c}$	$10^4\kappa$	λ_c	$\lambda_{corr.}$	Cell
500·0	22·36	164·2	328·4	360·3	*A*	25·00	5·000	9·583	383·3	390·7	*B*
250·0	15·81	87·06	348·2	371·2	*A*	20·00	4·472	7·693	384·6	391·3	*B*
125·0	11·18	45·24	362·2	378·6	*A*	12·50	3·535	4·827	386·2	391·3	*B*
100·0	10·00	36·87	368·7	383·5	*A*, *B*	10·00	3·162	3·864	386·4	391·1	*B*, *C*
62·27	7·905	23·15	371·6	383·2	*A*, *B*	5·00	2·236	2·002	397·4	400·7 *	*B*, *C*
50·00	7·071	18·89	377·8	388·4	*B*	2·50	1·581	1·007	402·8	405·2 *	*B*, *C*

* See text.

λ_∞ (graphical) = 398·0.

TABLE 4. $(CF_3)_2AsO \cdot OH$.

10^4c	$10^2\sqrt{c}$	$10^4\kappa$	λ_c	$\lambda_{corr.}$	Cell	10^4c	$10^2\sqrt{c}$	$10^4\kappa$	λ_c	$\lambda_{corr.}$	Cell
500·0	22·36	146·8	293·6	323·6	*A*	20·00	4·472	7·63	381·5	388·2	*B*
250·0	15·81	80·93	323·7	345·7	*A*	10·00	3·162	3·83	386·5	391·3	*B*
123·9	11·13	42·99	347·0	362·9	*B*	5·00	2·236	1·946	389·4	392·7	*B*
62·50	7·905	22·63	362·1	373·7	*B*	2·50	1·581	0·9747	389·9	392·2	*B*
40·00	6·324	14·94	373·5	382·8	*B*						

λ_∞ (graphical) = 399·5.

In Table 2, $\alpha(= \lambda_c/\lambda_x)$ was calculated from the equation $\lambda_x = \lambda_\infty (A + B\lambda_\infty)\sqrt{c\lambda_c/\lambda_x}$. Provisional values of λ_x were obtained for different concentrations, the quantity λ_x under the square-root sign being replaced by λ_∞. The approximate results for λ_x were then used in the $\sqrt{c\lambda_c/\lambda_x}$ term and a more accurate value of λ_x computed; this was continued until λ_x remained constant, and α was then calculated. Molecular weights were used as equivalent weights.

The accuracy of these results is not high, since the resistances measured were low, particularly for the carboxylic acids.

Attempted Preparation of Tristrifluoromethylarsine Oxide.—Tristrifluoromethylarsenic dichloride (1·75 g.) (*J.*, 1953, 1552), sealed with water (5 ml.) and left overnight at room temperature, gave tristrifluoromethylarsine (1·15 g., 85%) (Found: *M*, 281. Calc. for C_3F_9As:

M, 282). The solution was freeze-dried to give bistrifluoromethylarsinic acid (0·15 g.) [Found : CF_3(as CHF_3), 59·2; As, 29·3. Calc. for $C_2HO_2F_6As$: CF_3, 55·3; As, 30·5%] containing at most only a trace of tristrifluoromethylarsine oxide (Calc. for C_3OF_9As : CF_3, 69·6; As, 25·1%).

Tristrifluoromethylarsenic dichloride (2·88 g.), sealed with ethanol (5 ml.) at room temperature for 48 hr., gave tristrifluoromethylarsine (2·25 g., 98%) (Found : *M*, 281), identified by means of its infra-red spectrum.

TABLE 5. *Conductivities in acetic acid.*

(Cell *C* with resistances in parallel.)

10^4c	$10^2\sqrt{c}$	$10^3\kappa$	$10^2\lambda_c$	10^4c	$10^2\sqrt{c}$	$10^3\kappa$	$10^2\lambda_c$
CF_3·AsO(OH)$_2$				$(CF_3)_2$AsO·OH			
386·6	19·66	15·35	0·397	389·6	19·73	23·87	0·613
214·8	14·66	7·97	0·409	203·5	14·27	13·13	0·657
133·4	11·55	6·06	0·457	107·5	10·37	7·34	0·683
52·1	7·22	2·80	0·537	64·5	8·03	4·52	0·701
				38·8	6·23	2·61	0·721
CF_3·CO_2H				C_3F_7·CO_2H			
1000	31·62	5·12	0·051	1849	42·99	3·30	0·018
762·6	27·62	4·08	0·054	1361	36·89	2·27	0·016
465·2	21·57	2·70	0·058	652·0	25·54	1·33	0·020
256·0	16·00	1·70	0·066				

Tristrifluoromethylarsenic dichloride (1·3 g.) and glacial acetic acid (0·5 ml.), kept at 20° for 72 hr., gave chlorobistrifluoromethylarsine (0·9 g., 98%) (Found : *M*, 243. Calc. for C_2ClF_6As : *M*, 248) and chlorotrifluoromethane (0·3 g., 80%) (Found : *M*, 105. Calc. for $CClF_3$: *M*, 104·5).

Tristrifluoromethylarsenic dichloride (2·3 g.), shaken with silver oxide (1·5 g.) and water (5 ml.) for 24 hr. at 20°, gave carbon dioxide (0·205 g.) (Found : *M*, 45. Calc. for CO_2 : *M*, 44), identified tensimetrically, and chlorobistrifluoromethylarsine (0·21 g., 31%) (Found : *M*, 248). The aqueous solution was filtered and freeze-dried to give bistrifluoromethylarsinic acid (1·25 g., 78%) [Found : CF_3(as CF_3H), 55·3; As, 30·25. Calc. for $C_2HO_2F_6As$: CF_3, 55·3; As, 30·5%]. Fluoride (*ca.* 0·05 g.) was detected in the aqueous phase.

Reaction of Di-iodotrifluoromethylarsine with Methylmagnesium Iodide.—The Grignard reagent, prepared from methyl iodide (2·0 g.), ether (20 ml.), and magnesium (0·90 g.), was filtered and added dropwise (30 min.) with stirring and cooling to di-iodotrifluoromethylarsine (5·3 g.) in ether (10 ml.). Benzene (20 ml.) was added and the ether was removed by use of a water-bath at 60°. The benzene solution was shaken three times with 5N-hydrochloric acid (20 ml.) and then added to hydrogen peroxide (5 ml., 30%) and water (20 ml.). Examination of the aqueous layer failed to reveal methyl(trifluoromethyl)arsinic acid. The ethereal solution obtained as above was treated with mercuric chloride. The precipitate was washed with water, dried between filter-papers, and heated *in vacuo* to give *dimethyltrifluoromethylarsine* (0·067 g.), b. p. 58° (isoteniscope) (Found : CF_3, 39·0%; *M*, 172. $C_3H_6F_3As$ requires CF_3, 39·7%; *M*, 174), shown to be free from trimethylarsine, methylbistrifluoromethylarsine, and tristrifluoromethylarsine by its infra-red spectrum (C.S. No. 93). The compound was analysed as follows : 0·0623 g., sealed with 15% aqueous sodium hydroxide (20 ml.) and kept at 80° for 5 days, gave unchanged dimethyltrifluoromethylarsine (0·024 g., 38·1%). The fluoroform evolved was weighed (0·149 g.).

Reaction of Tristrifluoromethylarsine with Methyl Iodide.—This reaction (*J.*, 1952, 1552), carried out on a 0·2 molar scale, gave methylbistrifluoromethylarsine, b. p. 53°, in 50% yield. Attempts to prepare methyliodotrifluoromethylarsine by reaction of iodine with methylbistrifluoromethylarsine were unsuccessful.

Tristrifluoromethylarsine appears to form an equimolar azeotrope with methyl iodide, b. p. *ca.* 25° [Found : *M*, 206, 219. Calc. for $(CF_3)_3As,CH_3I$: *M*, 212]. It separates into two layers when cooled.

Infra-red Spectra.—These were recorded by a Perkin-Elmer Model 21 Spectrophotometer with rock salt optics.

One of us (R. C. P.) is indebted to the University of Punjab (India) for leave of absence, during which this work was carried out.

UNIVERSITY CHEMICAL LABORATORY
CAMBRIDGE.

[*Received, September 3rd*, 1953.]

Triterpenoids. Part XV. The Constitution of Icterogenin, a Physiologically Active Triterpenoid.*

By D. H. R. Barton and P. de Mayo.

[Reprint Order No. 4720.]

The constitution and stereochemistry of icterogenin, the jaundice-producing constituent of *Lippia rehmanni* Pears, have been elucidated. Icterogenin, $C_{35}H_{52}O_6$, is a carboxylic acid containing a ketone group, a free primary hydroxyl group, and also a secondary hydroxyl group esterified with angelic acid. Mild treatment with alkali provokes elimination of formaldehyde. On mechanistic grounds, confirmed by subsequent degradation, this shows that the primary hydroxylic function (CH_2·OH) is secured α with respect to the ketone grouping. The attachment of the angelic acid residue β with respect to the carboxyl group has been demonstrated by the appropriate hydrolysis, oxidation, and decarboxylation experiments. By alkali-induced elimination of the primary hydroxylic function and pyrolytic removal of the angeloyloxy-residue followed by hydrogenation, icterogenin methyl ester has been converted into methyl hedragonate.† Icterogenin methyl ester and methyl hederagonate † have been transformed into hexahydrobenzoates differing only in configuration at $C_{(4)}$.

This investigation is concerned with the jaundice-producing principle of *Lippia rehmanni* Pears (Rimington, Quin, and Roets, *Onderstepoort J. Vet. Sci.*, **1937**, **9**, 225). This compound, which has been named icterogenin, is one of the substances known to produce "*geeldikkop*" (yellow thick head), a complex syndrome including jaundice and photosensitivity in sheep. A probably related compound, lantadene A, with the same physiological activity, has been isolated by Louw (*ibid.*, 1943, **18**, 197; 1948, **23**, 233; 1949, **22**, 321, 329) from *Lantana camara* L.

The isolation of pure icterogenin and a preliminary survey of its chemistry were reported in the excellent paper by Rimington, Quin, and Roets (*loc. cit.*). Through the courtesy of Professor C. Rimington, to whom we express our best thanks, it became possible to undertake an extensive re-investigation of the chemistry of this compound, initially with material extracted from the leaves of the plant.

Rimington *et al.* (*loc. cit.*) originally reported the isolation of three icterogenins designated A, B, and C. We find that icterogenin C is a solvated form of icterogenin A. Icterogenin B was found by Rimington *et al.* to afford icterogenin A acetate on acetylation and, although we have not yet encountered icterogenin B, we believe that it is also a different crystal form of icterogenin A. The constitutional problem is therefore simplified to a consideration of the chemistry of icterogenin A, henceforth designated icterogenin.

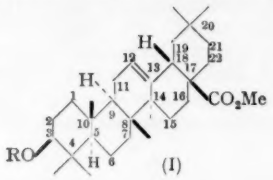
By extraction of *Lippia* leaves by the method of Rimington *et al.* (*loc. cit.*) icterogenin was obtained in small yield with constants in good agreement with those reported previously. Combustion data on icterogenin and its derivatives, as well as the extensive series of degradational experiments reported below, showed that the true molecular formula was $C_{35}H_{52}O_6$. In agreement with Rimington *et al.* (*loc. cit.*) the presence of a carboxyl group was shown by titration and by the preparation of a methyl ester. The equivalent, determined potentiometrically, was in satisfactory agreement with the above molecular formula. Likewise in agreement with the earlier work, the presence of a reactive carbonyl function was demonstrated by the formation of a 2 : 4-dinitrophenylhydrazone both by icterogenin and by its methyl ester. Since icterogenin was not a reducing substance it was tentatively, and correctly (see below), concluded that it was a ketone, not an aldehyde. The ultra-violet absorption spectra of the 2 : 4-dinitrophenylhydrazones were also in agreement with this view (cf. Braude and Jones, *J.*, 1945, 498). Acetylation of icterogenin gave an acetate with constants in agreement with those reported by Rimington *et al.* (*loc. cit.*).

* Part XIV, *J.*, 1953, 3111.

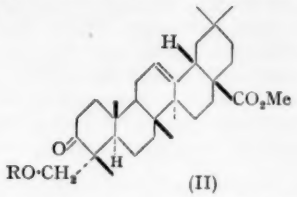
† It should be noted that the two slightly different names, methyl hederagonate and methyl hedragonate, represent different compounds, *viz.* (II; R = H) and (III), respectively.

As additional evidence for the presence of a hydroxyl group, a methyl ester acetate and a methyl ester benzoate, further characterised as the oxime, were prepared. The remaining two oxygen atoms of icterogenin could not be characterised directly, but were recognised to be part of an αβ-unsaturated ester or lactone function by the ultra-violet absorption spectrum [$\lambda_{max.}$ 212 mμ (ε 12,000)]. More extensive justification for this conclusion is presented later.

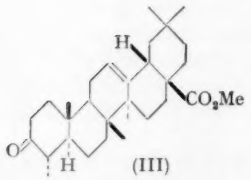
Pure icterogenin was initially available to us from the leaves of the plant only by wasteful fractional crystallisation. It seemed desirable therefore to seek alternative methods of purification. The study of these processes also had the added objective of confirming the homogeneity of icterogenin, a homogeneity concealed by the multiplicity of crystal forms. Chromatography of the methyl ester acetates gave the icterogenin derivative in only poor yield. From the earlier fractions, however, there was isolated in small amount methyl oleanolate acetate (I; R = Ac), the identity of which was confirmed by hydrolysis to methyl oleanolate (I; R = H). Even smaller quantities of a third



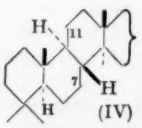
(I)



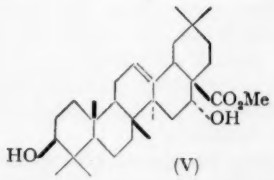
(II)



(III)



(IV)



(V)

component were also isolated. In contrast, chromatography of the methyl ester benzoates (cf. Brooks, Klyne, and Miller, *Biochem. J.*, 1953, **54**, 212) provided a convenient method of isolation and proof of homogeneity; much of the initial structural work was carried out, therefore, on icterogenin methyl ester benzoate. From the earlier fractions a small amount of methyl oleanolate benzoate (I; R = Bz) was isolated, whilst from later fractions two other apparently homogeneous compounds, also benzoates, were obtained, likewise in minor amount.

Attention was next directed to a determination of the number of ethylenic linkages in icterogenin. Palladium-catalysed hydrogenation of icterogenin in neutral solution afforded dihydroicterogenin. The latter showed no αβ-unsaturated function, in the ultra-violet absorption spectrum, but retained the functionally reactive carbonyl group. Similarly icterogenin methyl ester benzoate gave a dihydro-derivative characterised as the oxime. Further hydrogenation, with a platinum catalyst, furnished dihydroicterogenin methyl ester hexahydrobenzoate. Hydrogenation with a platinum catalyst in ethanol and acetic acid afforded tetrahydroicterogenin methyl ester hexahydrobenzoate, unchanged on further attempted hydrogenation. In the tetrahydro-derivative the carbonyl group had been reduced, as shown by the absence of a maximum at 280 mμ and the failure to give ketonic derivatives. All hydrogenated derivatives of icterogenin gave positive tetranitromethane tests indicating the retention of at least one non-hydrogenatable double bond. Titration of icterogenin methyl ester benzoate with perbenzoic acid gave indefinite results, but titration of the dihydro-derivative indicated the presence of only one ethylenic linkage. We were thus led to conclude that icterogenin had two ethylenic linkages, one of which was αβ-unsaturated to an ester or lactone group. On the former assumption there must, then, be five alicyclic rings. This conclusion was confirmed in the following way. Treatment of icterogenin with methanolic bromine gave a bromo-lactone, $C_{35}H_{51}O_6Br$, which regenerated its precursor on digestion with zinc dust and acetic acid. The bromo-lactone retained the

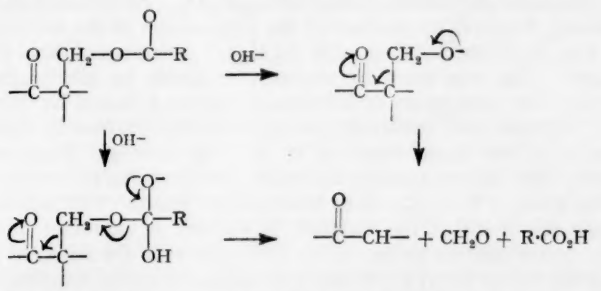
αβ-unsaturated function as shown by the ultra-violet absorption maximum at 218 mμ (ε 8400),* but no longer gave a colour with tetranitromethane. The bromo-lactone function must be derived from the unconjugated non-hydrogenatable ethylenic linkage, leaving the conjugated, but easily hydrogenated, ethylenic linkage untouched.

Degradation experiments on icterogenin were next attempted in an effort to inter-relate the various oxygenated functions. Attempted alkaline hydrolysis of icterogenin methyl ester benzoate under normal conditions gave only intractable amorphous products. Treatment in the cold with 4% aqueous-methanolic potassium hydroxide under carefully defined conditions furnished a high yield of a crystalline compound, m. p. 220°, $[\alpha]_D$ +93°, of the composition $C_{35}H_{52}O_5$, as well as formaldehyde and benzoic acid. The presence of the last-named was shown by isolation whilst the formaldehyde was detected by condensation with dimedone and by the chromotropic acid colour reaction. A similar elimination of formaldehyde was induced, in the same way, from icterogenin methyl ester acetate with concomitant formation of the same compound $C_{35}H_{52}O_5$. The latter retained the carbonyl group of icterogenin, shown by oxime formation, as well as the αβ-unsaturated ester function, but the original hydroxyl group had disappeared (failure of acylation or dehydration; no hydroxyl band in the infra-red). Palladium-catalysed hydrogenation gave a dihydro-derivative, $C_{35}H_{54}O_5$, m. p. 188°, $[\alpha]_D$ +86°, showing only isolated-double-bond absorption in the ultra-violet. The compound of m. p. 188° was also obtained from dihydroicterogenin methyl ester benzoate and hexahydrobenzoate under mild alkaline conditions. It was further characterised as the oxime and 2 : 4-dinitrophenylhydrazone and thus also retained intact the original ketonic grouping of icterogenin. That the presence of the latter functional group was a prerequisite for generation of formaldehyde was indicated by the failure of tetrahydroicterogenin methyl ester hexahydrobenzoate to eliminate formaldehyde under the usual conditions.

Icterogenin itself, treated under mild alkaline conditions, lost formaldehyde to give an acid, $C_{34}H_{50}O_5$, converted on methylation into the compound, m. p. 220°, referred to above. Palladium-catalysed hydrogenation afforded a dihydro-derivative, $C_{34}H_{52}O_5$, also obtained by elimination of formaldehyde from dihydroicterogenin. Methylation, as expected, gave the compound, m. p. 188°, referred to above.

The facts with regard to formaldehyde elimination seemed to find explanation in terms of a reversed aldol-type condensation, for example as in scheme (*A*).

(*A*)

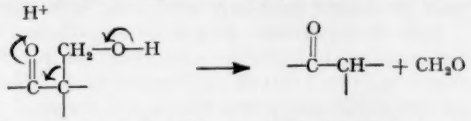


The following evidence provided support for this view. Although the compound, m. p. 220°, $C_{35}H_{52}O_5$, took up an indefinite amount of perbenzoic acid, its dihydro-derivative consumed only one mol., thus indicating only one unconjugated ethylenic linkage. The model compounds methyl hederagonate (II; R = H) and methyl hederagonate benzoate (II; R = Bz), on treatment under mild basic conditions identical with those applied to icterogenin, both gave methyl hedragonate (III) and formaldehyde. In the case of the

* The position of the maximum is displaced 6 mμ with resepct to that of icterogenin. The reason for this is that the maximum for the bromo-lactone represents the true maximum, whereas that reported for icterogenin itself is the summation of the band (at 218 mμ) due to the unsaturated ester function and that (at approx. 205 mμ on the sensitive Unicam S.P. 500 Spectrophotometer) due to the tri-substituted ethylenic linkage. The greater intensity of the maximum for icterogenin relative to that for the bromo-lactone illustrates also its composite character.

benzoate the formaldehyde was characterised both as the dimedone derivative and by the chromotropic acid colour test. In such compounds as methyl hederagonate elimination of formaldehyde can also be induced under acid conditions [mechanism (B)], as shown by the appropriate chromotropic acid test (see Experimental section). The elimination of formaldehyde from a similar system in a derivative of the triterpenoid asiatic acid during Wolff–Kishner reduction has been noted by Polonsky (*Compt. rend.*, 1951, **233**, 93, 671).

(*B*)



An even closer structural relationship to methyl hederagonate was suggested by the Zimmermann colour test (Zimmermann, *Z. physiol. Chem.*, 1935, **233**, 257; 1936, **245**, 47). We find that, amongst triterpenoid compounds with ketonic functions at position 3, 11, 12, 16, or 19 in the β-amyrin-type skeleton [see (I)] and at position 7 or 11 in the lanostane type skeleton [see (IV)], only those with the 3-keto-group give a colour. By applying this test to icterogenin and its derivatives, it was shown that the intensity and colour corresponded exactly to that observed with hederagonic acid and its derivatives, including methyl hedragonate (III). The positive Zimmermann test, coupled with the formaldehyde elimination, demonstrates the presence of the grouping (·CH_2·CO·C·CH_2·OH) in icterogenin and tentatively locates the keto-group at $C_{(3)}$ in an assumed triterpenoid skeleton.

Further experiments then revealed the nature of the postulated αβ-unsaturated ester function. Vigorous alkaline hydrolysis of the $C_{35}H_{54}O_5$ compound, m. p. 188° (see above), afforded a keto-alcohol, $C_{30}H_{46}O_4$, and a steam-volatile acid identified by its equivalent, by R_F value, and by preparation of the *p*-bromophenacyl ester, as α-methyl-*n*-butyric acid. Similar hydrolysis of the $C_{35}H_{52}O_5$ compound, m. p. 220° (see above), gave the same keto-alcohol and a steam-volatile acid identified by the ultra-violet absorption spectrum and by the *p*-bromophenacyl ester as tiglic acid. Five carbon atoms of icterogenin were thus accounted for as well as its αβ-unsaturated ester function. The postulate of five alicyclic rings also receives final confirmation.

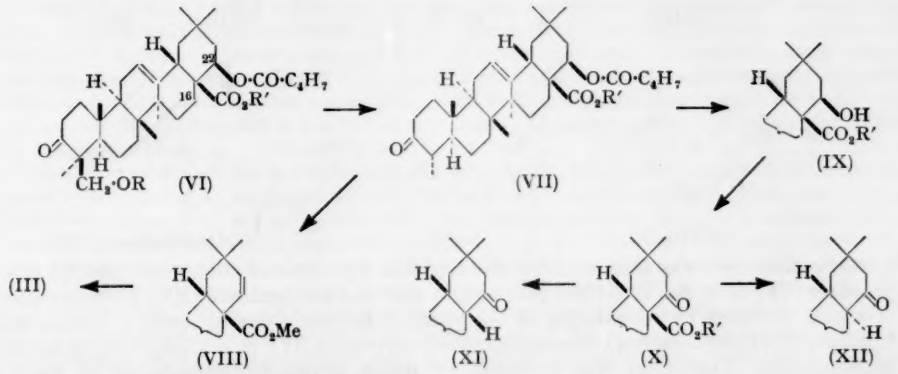
The keto-alcohol, $C_{30}H_{46}O_4$, was smoothly oxidised by chromic acid to a diketone, $C_{30}H_{44}O_4$, which on treatment with ethanolic potassium hydroxide gave, with concomitant hydrolysis and decarboxylation, a diketone $C_{28}H_{42}O_2$. An isomeric diketone was obtained in the following way. A by-product of the preparation of the keto-alcohol methyl ester, $C_{30}H_{46}O_4$, was the corresponding acid, $C_{29}H_{44}O_4$, reconverted into the methyl ester by diazomethane. This was more conveniently available by alkali-induced elimination of formaldehyde from icterogenin or dihydroicterogenin followed by more vigorous alkaline hydrolysis. Chromic acid oxidation gave an unstable diketo-acid which, when warmed in benzene solution, was decarboxylated to give the isomeric diketone, $C_{28}H_{42}O_2$. These results require that the unsaturated side-chain of icterogenin be attached through a secondary hydroxyl group β with respect to the carboxyl group. The formation of two isomeric C_{28} diketones requires that the carboxyl be tertiary in character in order to provide an asymmetric centre bearing an enolisable hydrogen α- to the adjacent ketone group. The environment of the carboxyl group was also indicated by the resistance of the methyl ester groups in icterogenin derivatives to alkaline hydrolysis. Thus the difficulty of hydrolysis was about the same as in methyl echinocystate (V). The hydrolysis was, however, easier than with methyl oleanolate (I; R = H). In both the former cases this must be due to facilitation by a β-hydroxyl group. One must conclude from these experiments that icterogenin contains the grouping $HO_2C\cdot\overset{|}{\underset{|}{C}}\cdot CH\cdot O\cdot CO\cdot CMe{:}CHMe$.

During the work outlined above a number of observations had been made which were indicative of a possible β-amyrin skeleton in icterogenin. The ready formation of a bromo-lactone is characteristic of oleanolic acid and its derivatives. The bromo-lactone from icterogenin had a γ-lactone band at 1786 cm.$^{-1}$, closely comparable with that (1779 cm.$^{-1}$) found by us for oleanolic bromo-lactone and that (1780 cm.$^{-1}$) for pyroquinovic bromo-lactone. Icterogenin is thus βγ- or γδ-unsaturated. The former possibility was rejected

since neither icterogenin nor any of its appropriate derivatives shows the ease of decarboxylation (cf. Barton and Brooks, *J.*, 1951, 257) characteristic of βγ-unsaturated acids. Icterogenin therefore contains the grouping ⟩C:C·C·C·CO$_2$H). The reactivity of the isolated ethylenic linkage of icterogenin towards per-acid and towards chromic acid was also indicative of a β-amyrin-type skeleton. Oxidation of the $C_{35}H_{54}O_5$ compound, m. p. 188° (see above), with chromic acid at room temperature gave an αβ-unsaturated ketone, $C_{35}H_{52}O_6$, $\lambda_{max.}$ 249 mμ. Under the same conditions β-amyrin benzoate afforded 11-oxo-β-amyrin benzoate, $\lambda_{max.}$ 249 mμ.

The presence of a β-amyrin-type carbon skeleton was conclusively established in the following way. The $C_{35}H_{52}O_5$ compound, m. p. 220° (see above), was pyrolysed at low pressure (see Experimental section) to give the corresponding olefin, $C_{30}H_{44}O_3$, by unimolecular ester elimination (cf. Barton, Head, and Williams, *J.*, 1953, 1715). Hydrogenation of this compound, followed by reoxidation of the reduced ketone grouping, gave a substance identified as methyl hedragonate (III).

The summation of the evidence described above, coupled with further considerations outlined in the sequel, now lead us to propose formula (VI; R = R′ = H) as the constitution of icterogenin. The compound, $C_{35}H_{52}O_5$, m. p. 220°, is therefore (VII; R′ = Me), the derived pyrolysis product, $C_{30}H_{44}O_3$, is (VIII), the hydroxy-ester, $C_{30}H_{46}O_4$, is (IX; R′ = Me), the diketo-ester, $C_{30}H_{44}O_4$, is (X; R′ = Me) and the two derived diketones are (XI) and (XII).



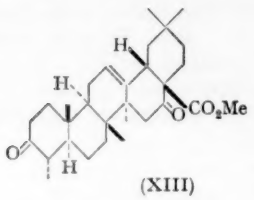
The isolation of tiglic acid as outlined above does not differentiate between a tiglate or an angelate side chain in icterogenin, since angelic acid is readily isomerised to tiglic acid. That the icterogenin side chain was in fact derived from angelic acid was shown by an examination of the acid produced in the pyrolysis of (VII; R′ = Me) (see above). This was shown to be pure angelic acid. Under the same pyrolytic conditions the thermodynamically more stable tiglic acid was, of course, recovered unchanged.

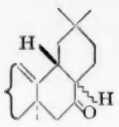
The work summarised above proves that the angelate side chain is secured β- with respect to the carboxyl group of icterogenin, but it does not distinguish between attachment at $C_{(16)}$ or at $C_{(22)}$. A decision in favour of $C_{(22)}$ is reached by exclusion. In their extensive work on the constitution of quillaic acid Kon and his collaborators (*J.*, 1939, 1130; 1940, 612, 1469; 1941, 552) prepared a diketo-ester (XIII), m. p. 193°, $[\alpha]_D$ +9°, which is clearly different from the corresponding icterogenin derivative [(X; R′ = Me), m. p. 234—235°, $[\alpha]_D$ +49°] although the methods of preparation of these two compounds as well as other considerations (see Experimental section) show that they both must have the more stable (α on the basis of conformational analysis: see Barton, *Experientia*, 1950, **6**, 316) configuration at $C_{(4)}$. Similarly the diketone (XIV) obtained by the alkali-induced conversion CO$_2$Me ⟶ H of (XIII) had m. p. 197°. The corresponding icterogenin derivative [(XI) or (XII)], although probably still a mixture of stereoisomers, had m. p. 220—226°.

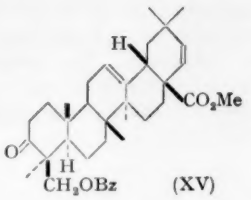
The configuration of the $C_{(22)}$ ester residue is regarded as β on the grounds that its

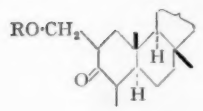
marked resistance to hydrolysis is more commensurate with the polar (β) than the equatorial (α) configuration (see Barton, *loc. cit.*; *J.*, 1953, 1027; Barton and Holness, *J.*, 1952, 78). This contention is supported by the fact that the keto-alcohol (IX; R′ = Me) was recovered unchanged after treatment with pyridine–acetic anhydride at room temperature overnight. So far as we are aware all equatorial hydroxyl groups are acetylated under these conditions.

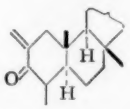
The configuration of the CH_2·OH residue of icterogenin was shown to be β on the following evidence. Vogel, Jeger, and Ruzicka (*Helv. Chim. Acta*, 1951, **34**, 2321) have used molecular-rotation arguments to show that the $C_{(4)}$-configuration in methyl hederagonate (II; R = H) must be α. The changes in molecular rotation on proceeding from methyl hederagonate and its benzoate (II; R = H and Bz respectively) to methyl hedragonate (III) are +86° and +275° respectively. The corresponding changes for icterogenin derivatives (VI; R = H, R′ = Me; and R = Bz, R′ = Me), are −80° and +95°. The discrepancies are large enough to suggest a difference in configuration, especially as optical anomalies (cf. Barton and Cox, *J.*, 1948, 783) should not be serious here. The postulated

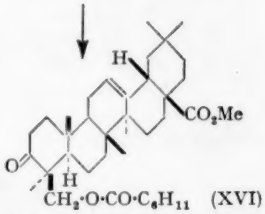

(XIII)


(XIV)


(XV)


(XVII)


(XVIII)


(XVI)

epimeric difference was confirmed by the fact that pyrolysis of icterogenin methyl ester benzoate (VI; R = Bz, R′ = Me) gave angelic acid and the benzoate (XV), hydrogenation of which, followed by reoxidation of the reduced ketonic grouping, gave a hexahydrobenzoate (XVI) *different* from the corresponding derivative (II; R = C_6H_{11}·CO·) of methyl hederagonate. The latter was prepared by direct hexahydrobenzoylation of methyl hederagonate. As would be expected both hexahydrobenzoates on treatment with aqueous-methanolic potassium hydroxide afforded methyl hedragonate (**III**).

The constitutional problem posed by icterogenin should not be left without mention of an alternative formulation (XVII; R = H) which could conceivably explain most of the relevant facts. This formulation is rejected (*a*) because it does not comply with the isoprene rule, (*b*) because treatment with alkali would be expected to give the methylene ketone (XVIII) (which would be negative in the Zimmermann test) rather than provoke the elimination of formaldehyde and (*c*) because pyrolysis of the appropriate benzoate (XVII; R = Bz) would also be expected to give compounds of the type (XVIII), especially as thermal elimination of benzoic acid occurs more readily that that of a lower aliphatic acid (cf. Barton and Rosenfelder, *J.*, 1949, 2459).

The infra-red spectra of icterogenin and many of its derivatives have been determined. It will be sufficient to state that these spectra are in consonance with the structures deduced as above on other evidence. The same applies to the internal consistency of the molecular-rotational correlations which can be made.

An examination of the roots of *Lippia rehmanni* revealed, in agreement with the earlier findings by Rimington *et al.* (*loc. cit.*), that these were a rich source of triterpenoid material. It proved impossible to obtain pure icterogenin simply by crystallisation, but by chromatography over silica gel (a procedure which should prove of general use in the fractionation of

triterpenoid carboxylic acids) it was possible to separate icterogenin from a new acid. In view of the origin of the latter we designate it rehmannic acid. It has the molecular formula $C_{35}H_{52}O_5$. The presence of a carboxyl group was indicated by its acidity and by the preparation of a methyl ester. A reactive carbonyl function was revealed by the preparation of an oxime and of a 2 : 4-dinitrophenylhydrazone. The position of the ultra-violet absorption maximum of the latter coupled with the non-reducing properties of the acid indicated that the carbonyl function was ketonic, not aldehydic. Work on the constitution of this acid is in progress and will be reported later.

Experimental

For general experimental conditions see Part VII (*J.*, 1952, 2339). Rotations were determined in chloroform solution, unless specified to the contrary. All ultra-violet absorption spectra (except those for 2 : 4-dinitrophenylhydrazones) were determined in ethanol solution with the Unicam S.P. 500 Spectrophotometer. Infra-red spectra were kindly determined by Messrs. Glaxo Laboratories Ltd. using, unless stated to the contrary, carbon disulphide as solvent. Silica gel for chromatography was obtained from Messrs. Hopkin and Williams Ltd.

Examination of the Leaves of Lippia rehmanni.—The dried powdered leaves (500 g.) were steeped in 95% ethanol (2 l.) overnight. After filtration the leaves were further extracted with a similar volume of alcohol. The combined filtrates were evaporated *in vacuo* to *ca.* 700 ml. Ether (2 l.) was then added and the mixture diluted to 5 l. with water. After separation of the ethereal layer the aqueous phase was re-extracted with a further quantity (1 l.) of ether. The combined ethereal extracts were washed twice with water and then shaken with sodium carbonate solution (2·5%; 15 ml.). The dark aqueous phase was separated (viewing by reflected light from a 100-w bulb is recommended) and the ether further extracted with sodium carbonate solution (6 × 25 ml.). All extracts except the first were combined. Occasionally some sodium salt separated; this was collected separately. The alkaline extracts were washed twice with ether, and a final layer of ether was added. Solid sodium chloride (25 g.) was introduced with stirring and the mixture left in the icebox overnight. The separated sodium salt was collected by filtration [0·65 g.; m. p. 225—300° (decomp.)].

The total combined sodium salts were dissolved in alcohol (10 ml.), acidified to Congo-red paper with hydrochloric acid, and diluted, when hot, with water until the solution was cloudy. Crude icterogenin (0·35 g.; m. p. 200—220°) gradually separated. Repeated recrystallisation from hot methanol afforded in poor yield a product, m. p. 239—241°, crystallising in short rods. This corresponded to the icterogenin A of Rimington *et al.* (*loc. cit.*); it gave no depression in m. p. on admixture with the original specimen (m. p. 239—240°). If the product was allowed to crystallise slowly from cold aqueous methanol it separated as fine needles, m. p. 155—160°. This corresponded to the icterogenin C of Rimington *et al.* (*loc. cit.*) and, in agreement, it gave no depression in m. p. on admixture with the original specimen (m. p. 155—160°). If the icterogenin C (either specimen) was kept for a short time at 140° it then melted at 239—240°, undepressed on admixture with icterogenin A. If the m. p. was determined in the usual way the melt resolidified at 160° and then remelted at 225—230°. Crystallisation of icterogenin A from cold aqueous methanol afforded icterogenin C, and recrystallisation of the latter in the usual way gave back icterogenin A.

Icterogenin, isolated in this way, and also from the roots of the plant (see below), had: (*A*) m. p. 239—241°, $[\alpha]_D$ +64° (*c*, 1·01), +63° (*c*, 0·84) (both in EtOH), +108° (*c*, 1·43), $\lambda_{max.}$ 212 mμ (ε 12,000); (*C*) m. p. 155—160°, $[\alpha]_D$ +63° (*c*, 1·07) (in EtOH) [Found, on material crystallised from benzene: C, 73·8; H, 9·1%; equiv., (potentiometrically) 562, (phenolphthalein) 555. $C_{35}H_{52}O_6$ requires C, 73·9; H, 9·2%; equiv., 569. Icterogenin was not a reducing substance as shown by tests with Fehling's solution and with Tollens's reagent.

Icterogenin, treated with pyridine–acetic anhydride at room temperature overnight, gave icterogenin acetate, m. p. (from methanol; plates) 155—168°, (from boiling aqueous ethanol; needles) 140—143°, $[\alpha]_D$ +56° (*c*, 1·12), +57° (*c*, 1·29). The latter crystal form and m. p. correspond to those reported by Rimington *et al.* (*loc. cit.*).

Icterogenin 2 : 4-dinitrophenylhydrazone, prepared in the usual way and crystallised from methanol (needles), had m. p. 244—246°, $\lambda_{max.}$ 365 mμ (ε 22,000 in $CHCl_3$) (Found: N, 7·2. $C_{41}H_{56}O_9N_4$ requires N, 7·5%).

Icterogenin, treated with diazomethane, gave the *methyl ester* (from methanol) as fine solvated needles, m. p. *ca.* 160° (with solvent evolution), $[\alpha]_D$ +102° (*c*, 1·40) (Found: C, 73·25; H, 9·75. $C_{36}H_{54}O_6,\frac{1}{2}CH_3{\cdot}OH$ requires C, 73·25; H, 9·35%).

Icterogenin methyl ester was converted into the 2 : 4-*dinitrophenylhydrazone* in the usual way. Recrystallised from acetone–light petroleum (b. p. 60—80°) this had m. p. 230—231° (Found : N, 7·5. $C_{42}H_{58}O_9N_4$ requires N, 7·35%).

Icterogenin acetate (see above), treated with diazomethane, afforded *icterogenin methyl ester acetate*. Recrystallised from methanol this had m. p. 161—163°, $[\alpha]_D$ +59° (*c*, 1·97), $\lambda_{max.}$ 214 mμ (ε 12,100) (Found : C, 71·5, 71·8; H, 9·25, 9·15. $C_{35}H_{56}O_7,CH_3{\cdot}OH$ requires C, 71·3; H, 9·2%).

Icterogenin methyl ester with pyridine–benzoyl chloride at room temperature overnight gave *icterogenin methyl ester benzoate*. Recrystallised from methanol this had m. p. 159—161°, $[\alpha]_D$ +60° (*c*, 0·95) ,+61° (*c*, 1·18), $\lambda_{max.}$ 228 mμ (ε 20,000) (Found : C, 75·45, 75·1; H, 8·3, 8·15. $C_{43}H_{58}O_7$ requires C, 75·2; H, 8·5%). The compound gave a yellow colour with tetranitromethane. The benzoate (50 mg.) was treated with an equal weight of hydroxylamine hydrochloride in pyridine at room temperature overnight. Crystallisation from methanol furnished the *oxime*, m. p. 221—223° (Found : C, 73·55; H, 8·2. $C_{43}H_{59}O_7N$ requires C, 73·55; H, 8·5%).

Icterogenin (30 mg.) in methanol (5 ml.) was treated with the theoretical amount of bromine in methanol solution (freshly prepared). The colour was rapidly discharged. The product of reaction was entirely neutral. Crystallisation from chloroform–methanol gave *icterogenin bromo-lactone*. This had m. p. 239—242° (decomp.), $[\alpha]_D$ +81° (*c*, 0·86), $\lambda_{max.}$ 218 mμ (ε 8,400) (Found : Br., 12·1. $C_{35}H_{51}O_6Br$ requires Br, 12·3%). The bromo-lactone gave no colour with tetranitromethane. The bromo-lactone (40 mg.) in " AnalaR " acetic acid (10 ml.) with addition of zinc dust (5 g.) was heated on the steam-bath with occasional shaking for 2 hr. Crystallisation of the product from aqueous methanol gave back icterogenin (m. p., mixed m. p., and negative Beilstein test).

Separation of Methyl Ester Benzoates.—The crude acids (20 g.), from the extraction of 7 kg. of powdered leaves by the process outlined above, were methylated with diazomethane, benzoylated (pyridine–benzoyl chloride at room temperature), and chromatographed over alumina (500 g.), to give 57 fractions. Elution with 1 : 1 benzene–light petroleum (b. p. 40—60°) (4 fractions; total 60 mg.) gave methyl oleanolate benzoate (from chloroform–methanol), m. p. 253—255°, $[\alpha]_D$ +84° (*c*, 1·30), undepressed in m. p. on admixture with an authentic specimen {m. p. 256—257°, $[\alpha]_D$ +85° (*c*, 1·10)}. Elution with 3 : 2 benzene–light petroleum (b. p. 40—60°) (4 fractions; total 30 mg.) gave a compound (from chloroform–methanol), m. p. 265—266° $[\alpha]_D$ −80° (*c*, 1·32) $\lambda_{max.}$ 228 mμ ($E^{1\%}_{1\,cm.}$ 314) (Found : C, 78·25; H, 8·7%). Elution with benzene gave material (3 fractions; total 75 mg.) which furnished a compound (from aqueous methanol), m. p. 219—222°, $[\alpha]_D$ +91° (*c*, 1·00), $\lambda_{max.}$ 228 mμ ($E^{1\%}_{1\,cm.}$ 400) (Found : C, 75·0; H, 8·05%). Elution with benzene and 19 : 1 benzene–ether (15 fractions) gave, after crystallisation from methanol, icterogenin methyl ester benzoate (see above) (2·2 g.). The homogeneity of this compound was further established by prolonged fractional crystallisation and by rechromatography.

Separation of Methyl Ester Acetates.—The crude acids (6·0 g.), from the extraction of 3 kg. of powdered leaves by the process outlined above, were methylated, acetylated (pyridine–acetic anhydride), and chromatographed over alumina (200 g.) to give 21 fractions. Elution with benzene (2 fractions; total 70 mg.) and crystallisation from chloroform–methanol gave methyl oleanolate acetate, m. p. 215—217°, $[\alpha]_D$ +71° (*c*, 1·02), undepressed in m. p. on admixture with an authentic specimen (m. p. 218°, $[\alpha]_D$ +70°). Hydrolysis with 5% methanolic potassium hydroxide gave methyl oleanolate, m. p. 195—196°, $[\alpha]_D$ +77° (*c*, 0·27), undepressed in m. p. on admixture with an authentic specimen (m. p. 195—196°, $[\alpha]_D$ +75°). Further elution with benzene (2 fractions; total 30 mg.) gave a compound (from chloroform–methanol), m. p. 243—244°, $\lambda_{max.}$ 216 mμ ($E^{1\%}_{1\,cm.}$ 270) (Found : C, 74·15, 73·6; H, 9·85, 9·05%). Further elution with benzene (6 fractions; total 1·01 g.) and repeated crystallisation from methanol gave, in poor yield only, icterogenin methyl ester acetate.

Examination of the Roots of Lippia rehmanni.—The finely powdered whole roots (10 kg.) were extracted with methanol (20 l.) as in the corresponding treatment of the leaves (see above). After three extractions the combined extracts were evaporated *in vacuo* to approx. 3 l. A heavy oil separated and, on cooling, the supernatant liquid could be decanted easily. The residue was almost entirely acidic and on crystallisation from chloroform–methanol gave mixed acids (10 g.) m. p. 253—256°, $[\alpha]_D$ +74° (*c*, 1·12 in EtOH), +103° (*c*, 2·35), not resolved by further crystallisation. Isolation of the acids from the supernatant liquid in the manner recorded above for treatment of the leaves gave a further 6 g. of mixed acids.

Although icterogenin and rehmannic acid could not be separated by crystallisation, the mixture (1·0 g.) was readily resolved on chromatography in benzene solution over silica gel

(80 g.) (15 fractions). Elution with 4 : 1 benzene–ether (five fractions; total 265 mg.) and crystallisation from methanol gave *rehmannic acid*, m. p. 295—300° (decomp.), $[\alpha]_D$ +84° (*c*, 1·05), $\lambda_{max.}$ 212 mμ (ε 12,400) (Found : C, 75·7; H, 9·25. $C_{35}H_{52}O_5$ requires C, 76·05; H, 9·5%). Elution with 1 : 1 benzene–ether (five fractions; total 575 mg.) and crystallisation from benzene afforded icterogenin, identical in all respects with that obtained from the leaves.

Rehmannic acid, treated with pyridine–hydroxylamine hydrochloride at room temperature overnight, afforded its *oxime*. Recrystallised from methanol this had m. p. 270—272° (decomp.) (Found : C, 73·95; H, 9·25. $C_{35}H_{53}O_5N$ requires C, 74·05; H, 9·4%).

Rehmannic acid was converted into the 2 : 4-*dinitrophenylhydrazone* in the usual way. Recrystallised from chloroform–methanol this had m. p. 273—274° (decomp.), $\lambda_{max.}$ 368 mμ (ε 21,000 in $CHCl_3$) (Found : C, 66·9; H, 7·55; N, 7·35. $C_{41}H_{56}O_8N_4$ requires C, 67·2; H, 7·7; N, 7·65%).

Methyl rehmannate was prepared from rehmannic acid (50 mg.) by methylation with diazomethane. Recrystallised from methanol in a solvated form this had m. p. *ca.* 140° (with evolution of solvent), $[\alpha]_D$ +86° (*c*, 1·37) (Found : C, 74·9; H, 9·9. $C_{36}H_{54}O_5,\frac{1}{2}CH_3{\cdot}OH$ requires C, 75·25; H, 9·7%).

Hydrogenation Products of Icterogenin.—Icterogenin (50 mg.) in ethyl acetate (10 ml.) was hydrogenated with a palladised charcoal catalyst (5%; 100 mg.) for 1 hr. Recrystallisation of the product from benzene gave *dihydroicterogenin*, m. p. 233—235°, $[\alpha]_D$ +126° (*c*, 1·07), no absorption max. at 212 mμ (Found : C, 73·6; H, 9·4. $C_{35}H_{54}O_6$ requires C, 73·65; H, 9·55%). There was a 10° depression in m. p. on admixture with icterogenin.

Icterogenin methyl ester benzoate (100 mg.) in ethanol (50 ml.) was hydrogenated with a palladised strontium carbonate catalyst (5%; 100 mg.) for 15 min. Recrystallisation of the product from methanol furnished *dihydroicterogenin methyl ester benzoate*, m. p. 180—182°, $[\alpha]_D$ +56° (*c*, 3·25) (Found : C, 74·85; H, 9·05. $C_{43}H_{60}O_7$ requires C, 74·9; H, 8·8%). This dihydrocompound (50 mg.), treated with pyridine–hydroxylamine hydrochloride overnight at room temperature, gave the *oxime*, m. p. 266—267° (from methanol) (Found : C, 73·15; H, 8·35. $C_{43}H_{61}O_7N$ requires C, 73·3; H, 8·75%). The benzoate and its oxime gave positive tetranitromethane tests.

Icterogenin methyl ester benzoate (20 mg.) in ethanol (50 ml.) was hydrogenated with a platinum catalyst (50 mg.) for 1 hr., to give *dihydroicterogenin methyl ester hexahydrobenzoate* (from aqueous methanol), m. p. 191—193°, $\lambda_{max.}$ 287 mμ (ε 30), no max. at 230 mμ (Found : C, 74·05; H, 9·4. $C_{43}H_{66}O_7$ requires C, 74·3; H, 9·55%), which gave a positive test with tetranitromethane.

Icterogenin methyl ester benzoate (70 mg.) in ethanol (50 ml.) was hydrogenated with a platinum catalyst (50 mg.) for 24 hr. Acetic acid (1 ml.) was then added and the mixture reduced for a further 15 min. Working up gave *tetrahydroicterogenin methyl ester hexahydrobenzoate* (from methanol), m. p. 200—202°, $[\alpha]_D$ +57° (*c*, 1·09), no carbonyl max. in the ultraviolet region (Found : C, 73·7; H, 10·05. $C_{43}H_{68}O_7$ requires C, 74·1; H, 9·85%), which gave a positive test with tetranitromethane.

Elimination of Formaldehyde in the Icterogenin Series.—Icterogenin methyl ester benzoate (100 mg.) in methanol (70 ml.) was treated with potassium hydroxide (4 g.) in water (30 ml.) and left overnight at room temperature. The deposited crystals (75 mg.) were almost pure *methyl* 22β-*angeloyloxyhedragonate*. Recrystallised from methanol, this had m. p. 220—221°, $[\alpha]_D$ +93° (*c*, 1·68), $\lambda_{max.}$ 212 mμ (ε 9000) (Found : C, 75·95; H, 9·45. $C_{35}H_{52}O_5$ requires C, 76·05; H, 9·5%). This compound gave a positive test with tetranitromethane. It was recovered unchanged after attempted acetylation, benzoylation, and dehydration (with pyridine–phosphorus oxychloride). The compound (50 mg.) was treated with pyridine–hydroxylamine hydrochloride overnight at room temperature, to give the *oxime* (from methanol), m. p. 219—221° (Found : C, 73·75; H, 9·4. $C_{35}H_{53}O_5N$ requires C, 74·05; H, 9·4%). The alkali treatment was repeated at reflux temperature for 30 min., but no crystalline product could be isolated.

Methyl 22β-angeloyloxyhedragonate (200 mg.) in ethanol (70 ml.) was hydrogenated with a palladised strontium carbonate catalyst (100 mg.) for 1 hr., to give *methyl* 22β-(α-*methyl*-n-*butyroyloxy*)*hedragonate*. Recrystallised from methanol this had m. p. 187—188° $[\alpha]_D$ +86° (*c*, 1·37), no αβ-unsaturated ester band in the ultra-violet region (Found : C, 75·5; H, 9·7. $C_{35}H_{54}O_5$ requires C, 75·75; H, 9·8%). It gave a positive test with tetranitromethane and was recovered unchanged on being refluxed in 1% methanolic potassium hydroxide. On treatment (40 mg.) with pyridine–hydroxylamine hydrochloride it afforded the corresponding *oxime* (from methanol), m. p. 205—207° (Found : C, 73·6; H, 9·35. $C_{35}H_{55}O_5N$ requires C, 73·45; H, 9·7%). The ketone gave its 2 : 4-*dinitrophenylhydrazone* (from chloroform–methanol), m. p. 236—238°,

$\lambda_{max.}$ 369 mμ (ε 24,400 in $CHCl_3$) (Found: C, 67·35; H, 7·65. $C_{41}H_{58}O_8N_4$ requires C, 67·0; H, 7·95%).

Dihydroicterogenin methyl ester benzoate (100 mg.) in methanol (36 ml.) was treated with potassium hydroxide (2·5 g.) in water (12 ml.) and left for 3 hr. Filtration of the deposited crystals in 1 : 1 benzene–light petroleum (b. p. 40—60°) solution through a short column of alumina and crystallisation from methanol furnished methyl 22β-(α-methyl-*n*-butyroyloxy)-hedragonate, identified by m. p., mixed m. p., and rotation. The identity was confirmed by conversion into the oxime and 2 : 4-dinitrophenylhydrazone (see above) and by the appropriate mixed m. p.s thereon.

Dihydroicterogenin methyl ester hexahydrobenzoate (6 mg.) in methanol (8 ml.) was treated with potassium hydroxide (400 mg.) in water (3 ml.) during 4 hr. The product, isolated with ether, was converted into the 2 : 4-dinitrophenylhydrazone which had m. p. (from chloroform–methanol) 229—233°, undepressed on admixture with the corresponding derivative (see above) of methyl 22β-(α-methyl-*n*-butyroyloxy)hedragonate.

Icterogenin methyl ester acetate (10 mg.), treated in the same way, gave methyl 22β-angeloyloxyhedragonate, identified by m. p. and mixed m. p. Tetrahydroicterogenin methyl ester hexahydrobenzoate (9 mg.), also treated in the same way, was recovered unchanged (m. p. and mixed m. p.).

Icterogenin (350 mg.) in aqueous methanol (70%; 200 ml.) containing potassium hydroxide (8 g.) was set aside for 3 hr. The product, isolated with ether, was chromatographed over silica gel (8 g.) in 8 fractions. Elution with 9 : 1 benzene–ether (2 fractions; total 200 mg.) gave 22β-*angeloyloxyhedragonic acid*. Recrystallised from methanol as plates, this had m. p. 256—259°, $[\alpha]_D$ +92° (*c*, 1·41) (Found: C, 75·4; H, 9·05. $C_{34}H_{50}O_5$ requires C, 75·8; H, 9·35%). Elution with 1 : 1 benzene–ether (2 fractions) gave back a small amount of unchanged icterogenin (m. p. and mixed m. p.). On methylation with diazomethane 22β-angeloyloxyhedragonic acid gave the known methyl ester (see above), identified by m. p. and mixed m. p.

22β-Angeloyloxyhedragonic acid (120 mg.) in ethyl acetate (20 ml.) was hydrogenated for 1 hr. with a palladised charcoal catalyst (5%; 100 mg.), to give 22β-(α-*methyl*-n-*butyroyloxy*)-*hedragonic acid*, plates (from methanol) m. p. 250—253°, $[\alpha]_D$ +96° (*c*, 1·34) (Found: C, 75·3; H, 9·6. $C_{34}H_{52}O_5$ requires C, 75·5; H, 9·7%). The same compound (m. p. and mixed m. p.) was obtained on subjecting dihydroicterogenin (10 mg.) to the alkaline conditions used with icterogenin. Methylation with diazomethane gave methyl 22β-(α-methyl-*n*-butyroyloxy)-hedragonate identical (m. p. and mixed m. p.) with the compound described under the same name above.

Elimination of Formaldehyde in the Hederagone Series.—Methyl hederagonate, m. p. 213—215°, $[\alpha]_D$ +78° (*c*, 1·12), +100° (*c*, 1·14 in $COMe_2$) (230 mg.) (Jacobs, *J. Biol. Chem.*, 1925, **63**, 631), was converted into the *benzoate* by the action of pyridine–benzoyl chloride overnight at room temperature. Recrystallised from methanol, this had m. p. 160—161°, $[\alpha]_D$ +32° (*c*, 2·18) (Found: C, 77·35; H, 8·75. $C_{38}H_{52}O_5$ requires C, 77·5; H, 8·9%).

Methyl hederagonate benzoate (100 mg.) in methanol (70 ml.) was treated with a solution of potassium hydroxide (4 g.) in water (30 ml.). After 45 min. the crystals deposited (61 mg.) were filtered off and recrystallised from methanol, to give methyl hedragonate (Jacobs and Gustus, *ibid.*, 1926, **69**, 641), identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +101° (*c*, 1·62), +102° (*c*, 1·11)}. The authentic specimen had $[\alpha]_D$ +102° (*c*, 1·08) and m. p. 203—205°. The m. p. is lower than that recorded by Jacobs and Gustus but chromatography and crystallisation failed to raise it.

Methyl hederagonate (43 mg.) in aqueous methanol (70%; 40 ml.) containing potassium hydroxide (1·5 g.) was set aside overnight at room temperature. The deposited crystals (24 mg.) gave, on crystallisation from methanol, methyl hedragonate, identified by m. p. and mixed m. p.; there was a pronounced m. p. depression on admixture with starting material.

Methyl hedragonate (200 mg.) in methanol (50 ml.) containing potassium hydroxide (2·5 g.) was refluxed with two mols. of formaldehyde for 4 hr. The product of reaction (part of which had separated; m. p. 270—275°) was an amorphous intractable solid even on chromatography. Methyl hedragonate treated similarly but without the addition of formaldehyde was recovered unchanged (m. p. and mixed m. p.).

Isolation of Benzoic Acid.—The mother-liquors remaining after the elimination of formaldehyde from icterogenin methyl ester benzoate (165 mg.) in the usual way (see above) were extracted with ether, and the ether discarded. The aqueous phase was then acidified and again extracted. Removal of the ether and crystallisation from hot water gave benzoic acid (14 mg.) identified by m. p., mixed m. p., and absorption spectrum.

Detection of Formaldehyde.—The aqueous–methanolic filtrate from the treatment of methyl hederagonate benzoate (see above) was acidified to Congo-red paper with sulphuric acid and then distilled. To the distillate dimedone (70 mg.) was added. After 30 min. the mixture was distilled to 20 ml. The dimedone–formaldehyde compound (12·3 mg., 24·8%) gradually separated. It was identified by m. p., mixed m. p., and crystal form (fine needles). A similar experiment on icterogenin methyl ester benzoate (25 mg.) likewise afforded the dimedone–formaldehyde compound. A control experiment, without addition of any triterpenoid compound, yielded none of the compound.

The elimination of formaldehyde was also detected by the chromotropic acid method (Bricker and Johnson, *Ind. Eng. Chem. Anal.*, 1945, **17**, 400). Solutions of methyl hederagonate (38·4 mg.), icterogenin (36·7 mg.), and icterogenin methyl ester benzoate (48·6 mg.), each in ethanol (10 ml.), were treated at 21° with ethanolic potassium hydroxide (10%; 10 ml.). At various intervals 1-ml. portions were withdrawn and added each to water (1 ml.) containing concentrated sulphuric acid (0·2 ml.) in a 15-ml. centrifuge tube. Chloroform (2 ml.) was added to each tube and, after mixing and centrifuging, the chloroform layer was withdrawn by pipette. A further 2 ml. of chloroform were added and the extraction procedure was repeated. The residual aqueous layer was then treated in the manner described by Bricker and Johnson (*loc. cit.*). Trial experiments with added formaldehyde (but no triterpenoid) served to demonstrate that the extraction and estimation technique was adequate for the determination of more than 90% of the formaldehyde present (as shown by the standard curve). Runs with no formaldehyde and no triterpenoid gave no chromotropic acid colour (relative to the control). Failure to remove triterpenoid material by the chloroform-extraction procedure (see above) gave fallacious results since the concentrated sulphuric acid used in the last stage of Bricker and Johnson's procedure provoked formaldehyde elimination by an acid-catalysed mechanism. Thus methyl hederagonate (2·3 mg.) in ethanol (1 ml.), treated with standard chromotropic acid–sulphuric acid reagent, gave formaldehyde (14%). The following results (in terms of % of formaldehyde eliminated) were obtained after leaving the various solutions in contact with the alkaline reagent (see above) for 5 min.: methyl hederagonate 17 ± 3, icterogenin 13 ± 3, and methyl icterogenin benzoate 7 ± 2%

Detection of α-Methyl-n-butyric and of Tiglic Acids.—Methyl 22β-(α-methyl-*n*-butyroyloxy)-hedragonate (see above) (250 mg.) in ethanolic potassium hydroxide (10%; 20 ml.) was refluxed for 3 hr. The resulting solution was diluted with water and separated, by ether-extraction, into neutral and acid fractions. The aqueous phase (acid fraction) was acidified with 50% aqueous sulphuric acid to pH 1—2 and distilled. The distillate consumed 0·048N-sodium hydroxide solution equivalent to 43 mg. of α-methyl-*n*-butyric acid (theor., 45·5 mg.). The distillate had no selective ultra-violet absorption above 205 mμ. A small portion of the acid was run on ascending partition chromatograms in *n*-butanol–1·5N-ammonia (method of Reid and Lederer, *Biochem. J.*, 1952, **50**, 60), development being with *p*-bromocresol-purple in ethanol–formaldehyde. The R_c of the volatile acid (where $R_c = \frac{R_F \text{ of volatile acid}}{R_F \text{ of } n\text{-butyric acid}}$) was found to be 1·45. Under the same conditions valeric acid had R_c 1·7 and *iso*valeric acid R_c 1·4. This suggested that the volatile acid was a branched C_5 acid, and this was confirmed by conversion of the remainder of the material into the *p*-bromophenacyl ester. This had m. p. (from aqueous methanol) 56—57°, undepressed on admixture with an authentic specimen of the *p*-bromophenacyl ester of α-methyl-*n*-butyric acid (Found: C, 52·65; H, 5·45. Calc. for $C_{13}H_{15}O_3Br$: C, 52·2; H, 5·05%). Higher and lower homologues have widely different compositions. The ester was depressed in m. p. by *ca.* 10° on admixture with the *p*-bromophenacyl ester (m. p. 68°) of *iso*valeric acid.

Methyl 22β-angeloyloxyhedragonate (200 mg.) was hydrolysed and the volatile acid distilled as in the procedure detailed above. The distillate contained acid equivalent to 25 mg. of tiglic acid (theor., 36·5 mg.) and showed $\lambda_{max.}$ 217 mμ (ε *ca.* 7000). The acid was converted into its *p*-bromophenacyl ester which, after two crystallisations from aqueous methanol, had m. p. 62—65°, melting at 67—69° on admixture with authentic ester (m. p. 69—70°) from tiglic acid, but at 55—58° on admixture with authentic ester (m. p. 68—69°) from angelic acid. A mixed m. p. curve of the two authentic esters was constructed as indicated (percentage of tiglate, m. p. range, median m. p.): 95%, 64—70°, 66·5°; 90%, 59—65°, 62·5°; 70%, 52—61°, 56·5°; 60%, 51—57·5°, 54·5°; 44%, 49—54°, 51·5°; 31%, 49—55·5°, 52°. This indicated that the ester isolated contained about 93% of the tiglate (Found: C, 52·0; H, 4·65. Calc. for $C_{13}H_{13}O_3Br$: C, 52·55, H, 4·4%).

Degradation of Methyl 22β-(α-Methyl-n-butyroyloxy)hedragonate.—The methyl ester (100 mg.) in ethanolic potassium hydroxide (4%; 20 ml.) was refluxed for 6 hr. The neutral product was

chromatographed over alumina (8 fractions). Elution with 1 : 1 benzene–light petroleum (b. p. 40—60°) (6 fractions) gave *methyl* 22β-*hydroxyhedragonate*. Recrystallised from methanol this either had m. p. 242—245° or (solvated form) *ca.* 110° (decomp.), $[\alpha]_D$ +90° (*c*, 1·25) (Found : C, 76·75; H, 9·5. $C_{30}H_{46}O_4$ requires C, 76·55; H, 9·85%). It gave a positive test with tetranitromethane. The same compound (m. p. and mixed m. p.) was obtained from the alkaline hydrolysis of methyl 22β-angeloyloxyhedragonate under the same conditions. The compound (23 mg.) was left with acetic anhydride and pyridine overnight at room temperature. Crystallisation of the product from chloroform–light petroleum gave unchanged starting material (m. p. and mixed m. p.).

22β-(α-Methyl-*n*-butyroyloxy)hedragonic acid (40 mg.), refluxed with the ethanolic potassium hydroxide in the same way (4%; 10 ml.) for 6 hr., gave 22β-*hydroxyhedragonic acid*. Recrystallised from methanol, this had m. p. 267—271° (decomp.), $[\alpha]_D$ +97° (*c*, 1·36) (Found : C, 76·0; H, 9·7. $C_{29}H_{44}O_4$ requires C, 76·25; H, 9·7%). The same compound, identified by m. p. and mixed m. p., was obtained by similar hydrolysis of 22β-angeloyloxyhedragonic acid and as the by-product in the hydrolysis of methyl 22β-(α-methyl-*n*-butyroyloxy)- and 22β-angeloyloxyhedragonate referred to above. Methylation with diazomethane gave methyl 22β-hydroxyhedragonate, identified by m. p. and mixed m. p.

Methyl 22β-hydroxyhedragonate (100 mg.) in " AnalaR " acetic acid (10 ml.) was treated with chromium trioxide (18 ml.) in the minimum of water and left at room temperature overnight. Chromatography of the product over alumina (2 g.; 7 fractions) gave *methyl* 22-*oxohedragonate*, eluted with 1 : 1 benzene–light petroleum (b. p. 40—60°) (6 fractions; all identical). Recrystallised from methanol this had m. p. 234—235°, $[\alpha]_D$ +49° (*c*, 1·03) (Found : C, 76·7; H, 9·75. $C_{30}H_{44}O_4$ requires C, 76·90; H, 9·45%). It gave a positive test with tetranitromethane. The m. p. was depressed to 185—188° on admixture with an authentic specimen of the diketo-ester (m. p. 193°) from quillaic acid (Elliott, Kon, and Soper, *J.*, 1940, 612). Both diketo-esters were recovered unchanged (m. p. and mixed m. p.) after 5 minutes' refluxing with 5% methanolic potassium hydroxide.

Methyl 22-oxohedragonate (70 mg.) was hydrolysed by refluxing ethanolic potassium hydroxide (20%; 10 ml.) for 2 hr. The product, which was entirely neutral, was chromatographed on alumina (2 g.). Elution with 2 : 5 benzene–light petroleum (b. p. 40—60°) gave the *more* stable diketone. Recrystallised from methanol this melted unsharply at 220—226° (Found : C, 81·0; H, 10·35. Calc. for $C_{28}H_{42}O_2$: C, 81·9; H, 10·3%). In view of probable inhomogeneity of this material and of its unsatisfactory carbon analysis an alternative approach was indicated as outlined below.

22β-Hydroxyhedragonic acid (65 mg.) in " AnalaR " acetic acid (3 ml.) was treated with chromium trioxide (11 mg.) in " AnalaR " acetic acid (1 ml.) at room temperature overnight. The product was separated into acid and neutral (trace) fractions, and the acid fraction in benzene (10 ml.) heated on the steam-bath to effect decarboxylation. Separation into acid and neutral fractions gave, in the latter fraction, the *less* stable diketone. Purified by filtration in benzene solution through alumina and crystallisation from methanol, this had m. p. 212—217°, $[\alpha]_D$ +51° (*c*, 0·96) (Found : C, 82·1; H, 10·25%). It gave a marked depression in m. p. on admixture with the *more* stable diketone reported above. There were similar marked depressions in m. p. on admixture of either of the diketones from icterogenin with the analogous diketone (m. p. 185°) from quillaic acid (Elliott, Kon, and Soper, *loc. cit.*).

Pyrolysis of Methyl 22β-*Angeloyloxyhedragonate.*—The ester (205 mg.) was pyrolysed by passage through a Pyrex glass tube (40 cm. × 11 mm.) at 500°/0·5—0·7 mm. in a stream of oxygen-free nitrogen (approx. ½ l. per hr. at room temperature and atmospheric pressure). The product (140 mg.) was refluxed with methanolic potassium hydroxide (5%; 10 ml.) for 2 hr. and the neutral material (133 mg.) chromatographed over alumina. In this way any unchanged angeloyloxy-compound was converted into a relatively strongly adsorbed alcohol. Elution with 1 : 1 benzene–light petroleum (b. p. 40—60°) afforded *methyl hedragon*-21-*enate*. Recrystallised from methanol, this had m. p. 190—191°, $[\alpha]_D$ +39° (*c*, 1·39) (Found : C, 79·3; H, 9·6. $C_{30}H_{44}O_3$ requires C, 79·6; H, 9·8%).

Methyl hedragon-21-enate (29 mg.) in " AnalaR " acetic acid (10 ml.) was hydrogenated overnight at room temperature with a platinum catalyst (50 mg.). After removal of the catalyst by filtration and of the acetic acid by evaporation under reduced pressure, the product was refluxed with methanolic potassium hydroxide (5%; 10 ml.) for 1 hr. The neutral material, in " AnalaR " acetic acid (1 ml.), was treated with chromium trioxide (4·3 mg.) in " AnalaR " acetic acid (1 ml.) at room temperature overnight. Filtration of the product in benzene through a short column of alumina and recrystallisation from methanol gave methyl hedragonate, m. p.

and mixed m. p. 200—203°, $[\alpha]_D$ +98° (*c*, 0·42). The identity was confirmed by conversion into the 2 : 4-dinitrophenylhydrazone (m. p. and mixed m. p.). The authentic specimen of *methyl hedragonate* 2 : 4-*dinitrophenylhydrazone* was recrystallised from chloroform–methanol and had m. p. 270° (Found : C, 67·9; H, 7·75; N, 8·7. $C_{36}H_{50}O_6N_4$ requires C, 68·1; H, 7·95; N, 8·85%).

Pyrolysis of Icterogenin Methyl Ester Benzoate.—The benzoate (500 mg.) was pyrolysed in 100 mg. batches as in the procedure outlined above. The pyrolysate was chromatographed over alumina (51 g. : 16 fractions). Elution with 1 : 1 benzene–light petroleum gave (10 fractions) *methyl* 4-epi*hederagon-21-enate benzoate*. Recrystallised from methanol this had m. p. 171—172°, $[\alpha]_D$ +3° (*c*, 1·52) (Found : C, 77·9; H, 8·55. $C_{38}H_{50}O_5$ requires C, 77·75; H, 8·6%). Elution with benzene (4 fractions) afforded unchanged (m. p. and mixed m. p.) icterogenin methyl ester benzoate (65 mg.).

Methyl 4-*epi*hederagon-21-enate benzoate (95 mg.) in " AnalaR " acetic acid (40 ml.) was hydrogenated overnight with a platinum catalyst. After crystallisation from light petroleum (b. p. 60—80°), the product (45 mg.) in " AnalaR " acetic acid (2 ml.) was treated with chromium trioxide (4·5 mg.) in the same solvent (0·5 ml.) overnight at room temperature, to give *methyl* 4-epi*hederagonate hexahydrobenzoate* (from methanol), m. p. 187°, $[\alpha]_D$ +42° (*c*, 1·02) (Found : C, 77·1; H, 10·0. $C_{38}H_{58}O_5$ requires C, 76·7; H, 9·85%). The hexahydrobenzoate (7 mg.) in aqueous methanol (70%; 10 ml.) containing dissolved potassium hydroxide (400 mg.) was left overnight at room temperature. Crystallisation of the product from aqueous methanol gave methyl hedragonate, identified by m. p. and mixed m. p. The m. p. was depressed by 40° on admixture with starting material.

Methyl Hederagonate Hexahydrobenzoate.—Hexahydrobenzoyl chloride (prepared from hexahydrobenzoic acid and thionyl chloride and purified by distillation *in vacuo*) (1·0 g.) was added to a solution of methyl hederagonate (1·0 g.) in pyridine (10 ml.), and the whole left overnight at room temperature. Chromatography of the product over alumina (22 g.; 10 fractions), and elution with 1 : 3 benzene–light petroleum (b. p. 40—60°), gave *methyl hederagonate hexahydrobenzoate*, rhombs [from light petroleum (b. p. 40—60°)], m. p. 154—155°, $[\alpha]_D$ +65° (*c*, 1·38) (Found : C, 76·55; H, 10·05%). This derivative of hederagonic acid, like the benzoate, could only be crystallised with difficulty even when carefully purified. The mixed m. p. with methyl 4-*epi*hederagonate hexahydrobenzoate was depressed to 134—140°. Treatment of the hexahydrobenzoate (10 mg.) with aqueous methanol (70%; 10 ml.) containing dissolved potassium hydroxide (400 mg.) overnight at room temperature afforded methyl hedragonate, identified by m. p. and mixed m. p.

Oxidation of Methyl 22β-(α-*Methyl*-n-*butyroyloxy*)*hedragonate with Chromic Acid.*—The ester (60 mg.) in " AnalaR " acetic acid (10 ml.) was treated with chromium trioxide (18 mg.) in " AnalaR " acetic acid (3 ml.) at room temperature overnight, to give *methyl* 22β-(α-*methyl*-n-*butyroyloxy*)-11-*oxohedragonate*. Recrystallised from methanol, this had m. p. 209—212°, $\lambda_{max.}$ 249 mμ (ε 8500) (Found : C, 73·7; H, 8·95. $C_{35}H_{52}O_6$ requires C, 73·9; H, 9·2%). When β-amyrin benzoate was oxidised under these conditions it likewise afforded 11-oxo-β-amyrin benzoate.

Perbenzoic Acid Titrations.—Derivatives of icterogenin were subjected to perbenzoic acid titration in chloroform solution at ice-box temperature in the usual way. The results are summarised in the Table.

Derivatives of icterogenin	Perbenzoic acid (M)	Perbenzoic acid (mols.) added	consumed 20 hr.	2 days	4 days
Icterogenin methyl ester benzoate	0·071	5	1·2	2·5	3·2
Dihydroicterogenin methyl ester benzoate	0·050	6	0·7	0·95	0·9
Methyl 22β-angeloyloxyhedragonate	0·071	6	0·8	2·0	2·6
Methyl 22β-(α-methyl-*n*-butyroyloxy)hedragonate	0·02	1·6	0·2	—	0·4 *

* 0·8 in 15 days.

Rates of Alkaline Hydrolysis.—The following esters were refluxed with ethanolic potassium hydroxide (20%; 10 ml.) for 3 hr. and the amount of hydrolysis determined by weighing the amounts of (non-volatile) acid produced. The amounts of ester taken are indicated in parentheses. Methyl echinocystate (18·5 mg.), 60%; methyl oleanolate (50 mg.), 5%; methyl 22β-(α-methyl-*n*-butyroyloxy)hedragonate (120 mg.), 60%.

Detection of Angelic Acid.—The volatile acids formed in the pyrolysis of (i) icterogenin methyl ester benzoate and (ii) methyl 22β-angeloyloxyhedragonate were collected in a U-tube cooled in

an alcohol–solid carbon dioxide bath in the form of beautiful crystals condensed on the walls of the U-tube just above the level of the refrigerant. Microscopically the crystals in each case resembled angelic acid. This was confirmed by a mixed m. p. determination. The m. p.s of the volatile acids and their mixed m. p.s with (*a*) angelic acid (m. p. 44°) and (*b*) tiglic acid (m. p. 64°) were respectively: (i) 38—42°, 39—43°, below room temp.; (ii) 38—41°, 39—43°, below room temperature. Tiglic acid, subjected to pyrolysis under the same conditions, was recovered in the U-tube unchanged (m. p. and mixed m. p.s with tiglic acid and with angelic acid).

The authentic angelic acid used in these experiments was prepared by the method of Buckles and Mock (*J. Org. Chem.*, 1950, **15**, 680).

Zimmermann Tests.—The method used was that of Callow, Callow, and Emmens (*Biochem. J.*, 1938, **32**, 1312). The compound (*ca.* 0·5 mg.) was dissolved in 1 ml. of 2N-potassium hydroxide in absolute ethanol and 1 ml. of 1% *m*-dinitrobenzene in absolute ethanol. After 10 min. the mixture was diluted to 10 ml. with absolute ethanol. Tested in this way icterogenin methyl ester benzoate, icterogenin, methyl 22β-angeloyloxyhedragonate, methyl hedragonate, methyl hederagonate, methyl oleanonate, and α-amyrenone all gave a violet colour which faded after dilution. No colour was developed by the following compounds: methyl 12-oxo-oleananolate acetate, 12-oxo-α-amyranyl benzoate, methyl 12 : 19-dioxo-18β-oleananolate (Barton, Holness, Overton, and Rosenfelder, *J.*, 1952, 3751), methyl 11-oxo-oleananolate acetate (Barton and Holness, *J.*, 1952, 78), 7 : 11-dioxolanostan-3β-yl acetate, and 16-oxo-28-norolean-12-ene (Bilham and Kon, *J.*, 1940, 1469).

We thank the Government Grants Committee of the Royal Society, the Central Research Fund of London University and Imperial Chemical Industries Limited for financial assistance. One of us (P. de M.) is grateful to the Colonial Products Research Council for a Research Studentship. We also thank cordially the Chief of the Division of Botany, Dept. of Agriculture of the Union of South Africa, Pretoria, South Africa, for the collection of plant material.

BIRKBECK COLLEGE, LONDON, W.C.1. [*Received, October 13th*, 1953.]

Triterpenoids. Part XVI. The Constitution of Rehmannic Acid.*

By D. H. R. BARTON and P. DE MAYO.

[Reprint Order No. 4799.]

The triterpenoid, rehmannic acid, isolated from the roots of *Lippia rehmanni* Pears, has been shown by degradation experiments parallel to those applied to icterogenin to be 22β-angeloyloxyoleanonic acid (deoxyicterogenin).

IN Part XV * the isolation of a new triterpenoid acid, rehmannic acid, $C_{35}H_{52}O_5$, was briefly reported. As already mentioned this compound, like icterogenin, possesses a functionally reactive ketone grouping. The ultra-violet spectrum of rehmannic acid was similar to that of icterogenin and thus suggested that the remaining two (uncharacterised) oxygen atoms were part of an αβ-unsaturated ester residue. An even closer relationship to icterogenin was indicated by identical Zimmermann and tetranitromethane colours. On the basis of these findings and of further evidence outlined in the sequel the constitution (I; R = H) was deduced for rehmannic acid.

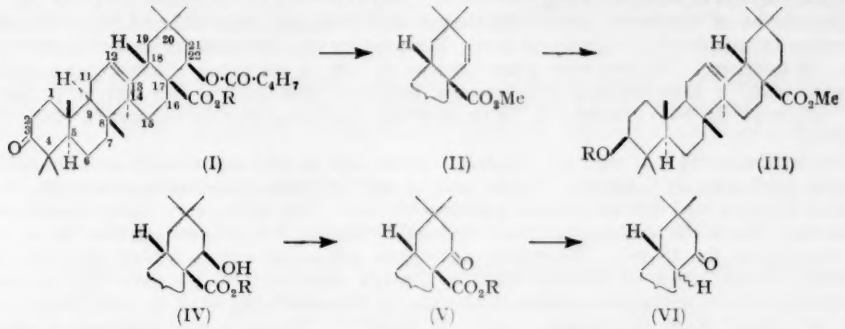
Pyrolysis of methyl rehmannate (I; R = Me) furnished angelic acid (thus confirming the presence of an αβ-unsaturated ester function as well as accounting for five of the carbon atoms of the parent compound) and an olefin (II). On hydrogenation, the latter afforded methyl oleanolate (III; R = H), further characterised as the acetate and the benzoate (III; R = Ac and Bz, respectively). All 35 carbon atoms of rehmannic acid are thus accounted for.

Vigorous alkaline hydrolysis of rehmannic acid furnished the corresponding hydroxy-acid (IV; R = H), chromic acid oxidation of which gave a β-keto-acid (V; R = H). The latter was not isolated but was characterised by its ready decarboxylation in warm benzene solution to a crystalline diketone, $C_{29}H_{44}O_2$ (VI), m. p. 237—240°, $[\alpha]_D$ +49°.

As with icterogenin, the placing of the ester side-chain at $C_{(22)}$ rather than at $C_{(16)}$ is based on exclusion evidence. Both the $C_{(17)}$ stereoisomeric nor-diketones, (VII) and

* Part XV, preceding paper.

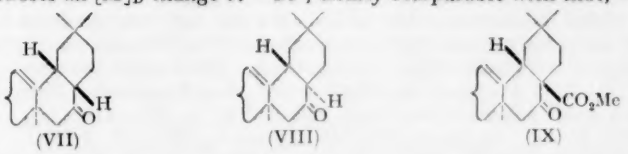
(VIII), have been obtained from echinocystic acid (White and Noller, *J. Amer. Chem. Soc.*, 1939, **61**, 983). These have m. p. 210—212°, $[\alpha]_D$ −93° (dioxan), and m. p. 230—233°, $[\alpha]_D$ +86°, and are clearly different from (VI). Indeed the diketone from rehmannic acid gave a m. p. depression on admixture with the latter compound. In agreement, conversion of (IV; R = H) into its methyl ester (IV; R = Me) and oxidation gave a diketo-methyl ester (V; R = Me), m. p. 197—199°, $[\alpha]_D$ +37°, different from the analogous echinocystic



(I) (II) (III) (IV) (V) (VI)

acid derivative (IX), of m. p. 166—168°, $[\alpha]_D$ +2° (dioxan) (White and Noller, *loc. cit.*) (see also Experimental).

The assignment of the β-configuration for the side-chain at $C_{(22)}$ is based in the main part on molecular-rotation considerations. Thus, it can be shown that the 22β-angeloyloxy-grouping of methyl icterogenin (see Part XV, *loc. cit.*) contributes +50° in $[M]_D$. Addition of this to the $[M]_D$ of methyl oleanonate (+417°; see Barton and Jones, *J.*, 1944, 659) gives a calculated $[M]_D$ of +467°, or $[\alpha]_D$ +83°, for the structure (I; R = Me). This is in close agreement with the observed $[\alpha]_D$ of +86° for methyl rehmannate. Further the conversion of methyl rehmannate into methyl dihydrorehmannate causes an $[M]_D$ change of −26°, clearly comparable with that, −37°, observed



(VII) (VIII) (IX)

in the reduction of methyl 22β-angeloyloxyhedragonate to the α-methyl-*n*-butyroyloxy-derivative. Other values which support this assignment are the increment for the hydrolysis of the angelate residue (−109° for the rehmannate series and −91° in the icterogenin series), and that for the oxidation of the 22β-hydroxyl to the ketone (−199° in the rehmannate series and −193° in the icterogenin series) (see Part XV, *loc. cit.*).

In the course of this work we prepared methyl deoxodihydrorehmannate and methyl deoxodihydroicterogenin benzoate. Details are given in the Experimental Section.

It is not without interest that the ultra-violet absorption spectrum of rehmannic acid ($\lambda_{max.}$ 212 mμ; ε, 12400), like that of icterogenin, corresponds to what would be expected from the superimposition of a β-amyrin-type of ethylenic linkage and of an angelate grouping rather than of a tiglate residue (see Adams and van Duuren, *J. Amer. Chem. Soc.*, 1953, **75**, 4631). Furthermore the absorption spectrum of icterogenin bromolactone (see Part XV, *loc. cit.*) is comparable with that of angelic acid rather than that of tiglic acid. Additional confirmatory evidence is thus forthcoming for the angelate side-chain in these compounds.

Experimental

For general experimental detail see Part VII (*J.*, 1952, 2339). Rotations were determined in chloroform solution. Ultra-violet absorption spectra were determined in ethanol solution, the Unicam S.P. 500 Spectrophotometer being used. M. p.s are uncorrected.

Methyl Dihydrorehmannate.—Rehmannic acid (110 mg.) in ethyl acetate (25 ml.) was hydrogenated for 1 hr., a palladised charcoal (50 mg.; 5%) catalyst being used. Crystallisation from methanol afforded *dihydrorehmannic acid*, m. p. *ca.* 160° (with solvent evolution), $[\alpha]_D$ +88° (*c*, 1·73), $\lambda_{max.}$ 282 mμ (ε, 30) (Found: C, 73·7; H, 9·75. $C_{35}H_{54}O_5,CH_3{\cdot}OH$ requires C, 73·7; H, 9·95%). Treatment with ethereal diazomethane gave *methyl dihydrorehmannate*, solvated needles (from methanol), m. p. *ca.* 125°, $[\alpha]_D$ +81° (*c*, 1·80) (Found: C, 76·15; H, 9·6. $C_{36}H_{56}O_5$ requires C, 76·0; H, 9·9%).

Degradation of Rehmannic Acid.—Rehmannic acid (100 mg.) was refluxed with ethanolic potassium hydroxide (4%; 10 ml.) for 6 hr. The product was chromatographed over silica gel (2 g.; 6 fractions). Elution with ether–benzene (1 : 19) (3 fractions) afforded 22β-*hydroxyoleanonic acid*. Recrystallised from aqueous methanol (fine needles) this had m. p. 233—236°, $[\alpha]_D$ +92° (*c*, 0·78) (Found: C, 74·1; H, 9·45. $C_{30}H_{46}O_4,CH_3{\cdot}OH$ requires C, 74·05; H, 10·05%).

The hydroxy-acid (101 mg.) in "AnalaR" acetic acid (3 ml.) was treated with chromium trioxide (15·5 mg.) in "AnalaR" acetic acid (1 ml.) at room temperature overnight. The product was separated into an acid and a neutral fraction. The latter (very small) fraction was discarded. The acidic fraction was decarboxylated by heating it in benzene solution (10 ml.) on the steam-bath for 15 min. Separation again into an acidic and a neutral fraction and filtration of the latter in benzene solution through alumina (1·0 g.) gave the *diketone*. Recrystallised from methanol as plates, this had m. p. 237—240°, $[\alpha]_D$ +49° (*c*, 1·06) (Found: C, 82·1; H, 10·55. $C_{29}H_{44}O_2$ requires C, 82·0; H, 10·45%). The m. p. was depressed to 210—217° on admixture of our sample with an authentic specimen of *iso*norechinocystenedione (White and Noller, *J. Amer. Chem. Soc.*, 1939, **61**, 983).

22β-Hydroxyoleanonic acid (see above) (35 mg.), with ethereal diazomethane, afforded the corresponding *methyl ester*. Recrystallised from methanol, this had m. p. 183—185°, $[\alpha]_D$ +78° (*c*, 1·02) (Found: C, 77·0; H, 10·3. $C_{31}H_{48}O_4$ requires C, 76·8; H, 10·0%).

Methyl 22β-hydroxyoleanonate (45 mg.) in "AnalaR" acetic acid (2 ml.) was treated with chromium trioxide (7 mg.) in "AnalaR" acetic acid (1 ml.) at room temperature overnight, giving *methyl 22-oxo-oleanonate*. Recrystallised from aqueous methanol, this had m. p. 197—199°, $[\alpha]_D$ +37° (*c*, 1·03); the m. p. was depressed to 145—153° on admixture of our sample with an authentic specimen of methyl 16-oxo-oleanonate (m. p. 169°) from echinocystic acid (White and Noller, *loc. cit.*) (Found: C, 76·9; H, 9·2. $C_{31}H_{46}O_4$ requires C, 77·15; H, 9·6%).

Pyrolysis of Methyl Rehmannate.—The methyl ester (280 mg.) was pyrolysed at 530°/1 mm. in three batches under the general conditions specified in Part XV (*loc. cit.*). The pyrolysate was chromatographed over alumina (11 g.); (8 fractions). Elution with benzene–light petroleum (b. p. 40—60°) (3 : 7) (2 fractions) furnished *methyl olean-21-enonate*. Recrystallised (with difficulty) from a small volume of methanol, this had m. p. 117—119°, $[\alpha]_D$ +19° (*c*, 1·28) (Found: C, 79·2; H, 9·6. $C_{31}H_{46}O_3,\frac{1}{2}CH_3{\cdot}OH$ requires C, 78·6; H, 9·85%). Elution with benzene–light petroleum (b. p. 40—60°) (3 : 2) (3 fractions) gave unchanged methyl rehmannate (m. p. and mixed m. p.).

Methyl olean-21-enonate (12 mg.) in "AnalaR" acetic acid (5 ml.) was hydrogenated at room temperature overnight, a platinum catalyst (50 mg.) being used. The catalyst was removed by filtration and the acetic acid by evaporation *in vacuo*. The residue was treated with methanolic potassium hydroxide (5%; 5 ml.) under reflux for 20 min. and the neutral product was crystallised from aqueous methanol, giving methyl oleanolate, m. p. 198—200°, $[\alpha]_D$ +70° (*c*, 0·7), undepressed in m. p. on admixture with an authentic specimen. Acetylation with pyridine–acetic anhydride at room temperature overnight gave methyl oleanolate acetate (m. p. and mixed m. p.).

In a second experiment the identity of the oleanolate was further confirmed by conversion into the benzoate (pyridine–benzoyl chloride at room temperature overnight). This had m. p. 260—261° (Kofler block), $[\alpha]_D$ +82° (*c*, 0·74), m. p. undepressed on admixture with an authentic specimen of the same m. p. and rotation. The acid resulting from the pyrolysis which collected in the cooled receiver was identified by m. p. (42°), mixed m. p., and crystal form as angelic acid (cf. Part XV, *loc. cit.*).

Methyl Deoxodihydrorehmannate.—Methyl dihydrorehmannate (see above) (67 mg.) in benzene (1 ml.) and toluene-ω-thiol (1 ml.) was shaken with perchloric acid (5 drops; 70%) (see Barton and Rosenfelder, *J.*, 1951, 1048) for 15 min. Crystallisation of the product from chloroform–methanol afforded the *dithioketal*, m. p. 183—185° (Found: C, 75·5; H, 9·0. $C_{50}H_{70}O_4S_2$ requires C, 75·15; H, 8·85%). The dithioketal (60 mg.) in purified dioxan (10 ml.) was refluxed with Raney nickel (5 g.) for 2 hr., giving *methyl deoxodihydrorehmannate*, m. p. 166—

168° (from methanol), $[\alpha]_D$ +100° (Found: C, 78·05; H, 10·2. $C_{36}H_{58}O_4$ requires C, 77·95; H, 10·55%).

Methyl Deoxodihydroicterogenin Benzoate.—Methyl dihydroicterogenin benzoate (270 mg.) in benzene (10 ml.) and toluene-ω-thiol (2 ml.) was shaken with perchloric acid (1 ml.; 70%) for 15 min. Crystallisation from chloroform–methanol gave the dithioketal (150 mg.), m. p. 168—170°. This was dissolved in dioxan (10 ml.) and refluxed with Raney nickel (5 g.) for 2 hr., giving *methyl deoxodihydroicterogenin benzoate*, fine needles (from chloroform–methanol), m. p. 192—193·5°, $[\alpha]_D$ +113° (*c*, 1·96), $\lambda_{max.}$ 229 mμ (ε, 15,500) (Found: C, 76·55; H, 9·0. $C_{43}H_{62}O_6$ requires C, 76·5; H, 9·25%).

We thank the Government Grants Committee of the Royal Society, the Central Research Fund of London University, and Imperial Chemical Industries Limited for financial assistance. One of us (P. de M.) is grateful to the Colonial Products Research Council for a Research Studentship.

BIRKBECK COLLEGE, LONDON, W.C.1. [*Received, November 14th,* 1953.]

Triterpenoids. Part XVII. The Transformation of Lanostadienol (Lanosterol) into 14-Methylcholestan-3β-ol.†*

By D. H. R. BARTON, D. A. J. IVES, and B. R. THOMAS.

[Reprint Order No. 4800.]

Lanostanol has been transformed, by stepwise contraction and expansion of ring A, into 14-methylcholest-4-en-3-one and thence into 14-methylcholestan-3β-ol. An alternative route for the modification of the triterpenoid ring A has been explored. Molecular-rotation data are briefly discussed.

THIS paper is concerned with continued studies on the conversion of the triterpenoid lanostadienol (I) into 14-methylated steroids (cf. Barton and Thomas, *Chem. and Ind.*, 1953, 172; *J.*, 1953, 1842; Voser, Heusser, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1953, **36**, 299).

Treatment of lanostanol (II) (Voser, Montavon, Günthard, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1950, **33**, 1893; McGhie, Pradhan, and Cavalla, *J.*, 1952, 3176) with phosphorus pentachloride afforded the olefin (III), which on ozonolysis at −60° furnished the derived ketone, 14-methyl-A-norcoprostan-3-one (IV). This showed an infra-red maximum at 1738 cm.$^{-1}$ (five-ring ketone) in agreement with the assigned constitution. Ring expansion of this compound was achieved by the elegant procedure of Voser, White, Heusser, Jeger, and Ruzicka (*Helv. Chim. Acta*, 1952, **35**, 830). Reaction with excess of methylmagnesium iodide gave the tertiary alcohol (V). This was not crystalline, so it was at once dehydrated with fuller's earth to furnish a mixture of olefins containing (VI). Treatment of the olefin mixture with osmium tetroxide followed by cleavage of the derived osmate with lithium aluminium hydride gave the crystalline glycol (VII). We would emphasise the use of lithium aluminium hydride in this connection, as it provides a more convenient method of processing osmates than those currently in use: it has been employed by us on a number of occasions. Fission of the glycol (VII) with lead tetra-acetate followed by base-catalysed cyclisation afforded the desired 14-methylcholest-4-en-3-one (VIII), characterised as the 2 : 4-dinitrophenylhydrazone.

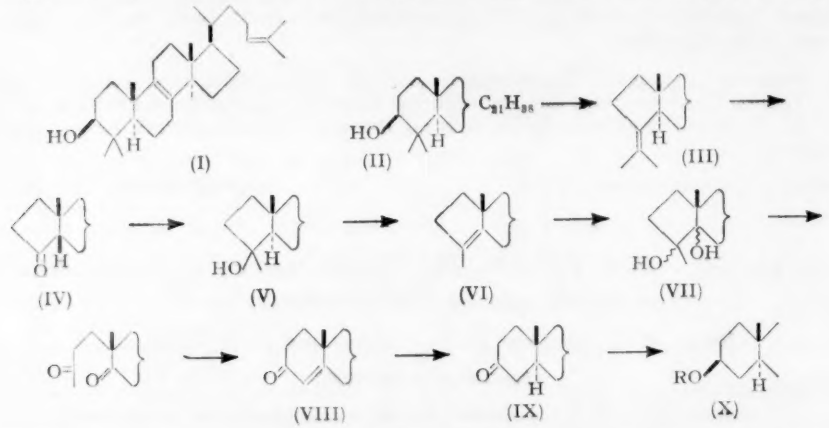
Preliminary experiments showed that reduction of cholest-4-en-3-one by lithium and liquid ammonia (Wilds and Nelson, *J. Amer. Chem. Soc.*, 1953, **75**, 5360) gave a good yield of cholestanone and that similar reduction of stigmasta-4 : 22-dien-3-one and of ergosta-4 : 22-dien-3-one likewise afforded satisfactory routes to stigmast-22-en-3-one (Barton and Brooks, *J. Amer. Chem. Soc.*, 1950, **72**, 1633) and ergost-22-en-3-one (Barton, Cox, and Holness, *J.*, 1949, 1771) respectively. By this method (VIII) was smoothly reduced to

* Part XVI, preceding paper.

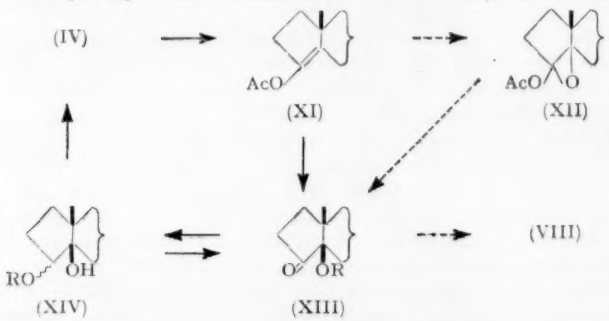
† The results in part have been summarised in a preliminary communication (*Chem. and Ind.*, 1953, 1180).

14-methylcholestan-3-one (IX), whence by lithium aluminium hydride reduction the desired 14-methylcholestan-3β-ol (X; R = H), characterised as the acetate, was obtained. The configuration assigned is based on molecular-rotation considerations (see below) and upon sound analogy (Shoppee and Summers, *J.*, 1950, 687).

We have taken the occasion to explore an alternative route for the conversion of the triterpenoid ring A into the Δ^4-3-one system characteristic of many physiologically



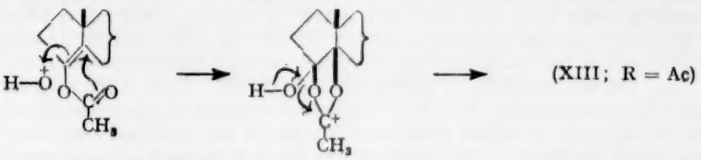
important steroids. Treatment of 14-methyl-A-norcoprostan-3-one (IV) with acetic anhydride and perchloric acid in carbon tetrachloride (Barton, Evans, Hamlet, Jones, and Walker, *J.*, 1954, 747) gave the derived enol acetate (XI), showing characteristic bands in the infra-red at 1760 and 1204 cm.$^{-1}$. It was then intended to follow the route indicated by the broken arrows, which is based in part on the elegant process of Kritchevsky, Garmaise, and Gallagher, *J. Amer. Chem. Soc.*, 1952, **74**, 483) for the elaboration of the



adrenocortical side chain. However treatment of (XI) with perphthalic acid afforded, with uptake of one mol. of oxidant, not the expected epoxide (XII), but a compound shown to have the rearranged structure (XIII; R = Ac) on the basis of the following evidence.* The ultra-violet absorption spectrum showed a distinct ketonic band at 303 mμ (ε 80), not altered on repeated fractionation. The infra-red spectrum revealed a broad, unsymmetrical, band at 1760 cm.$^{-1}$ indicative, by its intensity, of an acetate and of a *cyclo*pentanone, one or both bands being somewhat displaced. The presence of the acetate residue was confirmed by a band at 1232 cm.$^{-1}$. Attempted alkaline hydrolysis gave only amorphous products, but reduction with lithium aluminium hydride furnished the glycol (XIV; R = H), converted into the monoacetate (XIV; R = Ac) by pyridine–

* Dr. T. F. Gallagher of the Sloan-Kettering Institute for Cancer Research (New York) has very kindly informed us that he has observed an analogous rearrangement in the steroid series.

acetic anhydride. Oxidation of (XIV; R = H) with chromic acid afforded the keto-alcohol (XIII; R = H), which was recognised as a *cyclo*pentanone (infra-red maximum at 1740 cm.$^{-1}$) and as a tertiary alcohol (infra-red maxima at 3620 and 3500 cm.$^{-1}$; resistance to chromic acid oxidation). Acetylation of this keto-alcohol with acetic anhydride–perchloric acid gave (XIII; R = Ac), identical with the compound obtained directly from (XI); similar treatment of (XIV; R = H) furnished, not unexpectedly, the parent *cyclo*pentanone (IV). Attempts to convert (XIII; R = H or Ac) into (VII) and



thence into (VIII) by using either methylmagnesium iodide or methyl-lithium have not, so far, proved efficacious. The assignment of the β-configuration to the $C_{(5)}$-hydroxyl group in (XIII and XIV; R = H) is based on molecular-rotation considerations (Klyne, *J.*, 1952, 2916). The interesting rearrangement disclosed by our experiments presumably proceeds according to the annexed scheme.

The availability of 14-methylated steroids suggests that a comparison of molecular rotations might prove instructive. The data summarised in the Table show that, as would be expected from our previous work (Barton and Cox, *J.*, 1948, 783), significant vicinal effects can only be detected in the case of the 14-methylcholest-4-en-3-one (VIII).

	$[M]_D$						
Alcohol	Alcohol	Acetate	Derived 3-one	Derived Δ^4-3-one	Δ_1	Δ_2	Δ_3
Cholestan-3β-ol [a]	+ 89°	+ 60°	+162°	+357°	−29°	+73°	+268°
14-Methylcholestan-3β-ol [b]	+157	+120	+244	+460	−37	+87	+303

[a] Barton and Cox, *J.*, 1948, 783. [b] Experimental section.

14-Methylcholestenone has also been prepared independently of our work by Dr. O. Jeger and his collaborators in the laboratories of the Eidgenossische Technische Hochschule, Zürich. We express our cordial appreciation to Dr. Jeger for this information.

Experimental

For general experimental see Part VII (*J.*, 1952, 2339). Rotations were determined in $CHCl_3$ solution. All ultra-violet absorption spectra were taken in ethanol solution, with a Unicam S.P. 500 Spectrophotometer. Infra-red spectra were kindly determined by Messrs. Glaxo Laboratories Ltd., using carbon disulphide as solvent.

14-*Methyl*-3-iso*propylidene*-A-*norcholestane* (III).—Lanostanol (1·1 g.) in light petroleum (b. p. 60—80°) (100 ml.) was stirred at 0° with phosphorus pentachloride (700 mg.) for 30 min. Filtration of the product in light petroleum (b. p. 40—60°) through alumina gave 14-*methyl*-3-iso*propylidene* A-*norcholestane* (III) (800 mg.). Recrystallised from chloroform–methanol, this had m. p. 110—112°, $[\alpha]_D$ +33° (*c*, 2·2) (Found: C, 87·05; H, 12·5. $C_{30}H_{52}$ requires C, 87·3; H, 12·7%).

14-*Methyl*-A-*norcoprostan*-3-*one* (IV).—The above-mentioned olefin (200 mg.) in methylene dichloride (20 ml.) at −60° was ozonised until the solution no longer gave a colour with tetranitromethane, then was diluted with acetic acid (5 ml.) and stirred with zinc dust at 0°. The product was filtered in benzene solution through alumina, to give 14-*methyl*-A-*norcoprostan*-3-*one* (IV) (170 mg.). Recrystallised from methanol this had m. p. 124—125°, $[\alpha]_D$ +142° (*c*, 1·7) (Found: C, 83·8; H, 12·05. $C_{27}H_{46}O$ requires C, 83·85; H, 12·0%).

3 : 14-*Dimethyl*-A-*norcholestane*-3 : 5-*diol* (VII).—14-Methyl-A-norcoprostan-3-one (1·0 g.) was treated with methylmagnesium iodide and the product dehydrated with activated fuller's earth according to the directions of Voser *et al.* (*loc. cit.*). The resulting olefinic material (370 mg.) was treated with osmium tetroxide (250 mg.) in dry ether (50 ml.) for 24 hr. at room temperature. Excess of lithium aluminium hydride in ethereal solution was added and the mixture refluxed on the steam-bath for 2 hr., to give 3 : 14-*dimethyl*-A-*norcholestane*-3 : 5-*diol*

(VII), m. p. 155—157° (from methanol), $[\alpha]_D$ +35° (*c*, 1·6) (Found: C, 80·15; H, 11·75. $C_{28}H_{50}O_2$ requires C, 80·3; H, 12·05%).

14-Methylcholest-4-en-3-one (VIII).—3 : 14-Dimethyl-A-norcholestane-3 : 5-diol (100 mg.) in acetic acid (5 ml.) containing lead tetra-acetate (140 mg.) was left at room temperature. The uptake of 1 mol. of the oxidant was complete within 30 min. The product was treated with sodium methoxide in methanol (25 ml.; 3%) for 2 hr. at room temperature, the cyclisation of the intermediate diketone being followed spectroscopically. Chromatography over alumina and elution with 9 : 1 benzene–ether afforded *14-methylcholest-4-en-3-one* (30 mg.). Recrystallised from methanol this had m. p. 113—114°, $[\alpha]_D$ +116° (*c*, 1·0), $\lambda_{max.}$ 241 mμ (ε 14,500) (Found: C, 83·95; H, 11·5. $C_{28}H_{46}O$ requires C, 84·35; H, 11·6%). The derived *2 : 4-dinitrophenylhydrazone*, prepared in the usual way and recrystallised from chloroform–methanol, had m. p. 240—241°, $\lambda_{max.}$ 392 mμ (in $CHCl_3$; ε 21,000) (Found: N, 9·7. $C_{34}H_{52}O_4N_4$ requires N, 9·65%).

14-Methylcholestan-3β-ol (X; R = H).—14-Methylcholest-4-en-3-one (see above) (100 mg.) in dry ether (20 ml.) was added to a solution of lithium (50 mg.) in liquid ammonia (50 ml.) and the solution stirred for 20 min. Filtration of the product through alumina and elution with 1 : 1 light petroleum (b. p. 40—60°)–benzene gave *14-methylcholestan-3-one* (IX) (70 mg.). Recrystallised from chloroform–methanol, this had m. p. 161—162°, $[\alpha]_D$ +61° (*c*, 1·33) (Found: C, 83·6; H, 12·25. $C_{28}H_{48}O$ requires C, 83·9; H, 12·1%).

Reduction of this ketone (250 mg.) in dry ether (20 ml.) with lithium aluminium hydride (250 mg.) in the same solvent (40 ml.) under reflux for 2 hr. gave *14-methylcholestan-3β-ol* (X; R = H), m. p. 144—145° (from methanol), $[\alpha]_D$ +39° (*c*, 1·29) (Found: C, 83·3; H, 12·6. $C_{28}H_{50}O$ requires C, 83·5; H, 12·5%). Treatment with pyridine–acetic anhydride on the steam bath for 1 hr. gave the corresponding *acetate* (X; R = Ac), m. p. 98—99° (from aqueous ethanol), $[\alpha]_D$ +27° (*c*, 1·23) (Found: C, 81·2; H, 12·0. $C_{30}H_{52}O_2$ requires C, 81·0; H, 11·8%).

14-Methyl-A-norcholest-3(5)-en-3-yl Acetate (XI).—14-Methyl-A-norcoprostan-3-one (see above) (500 mg.) in carbon tetrachloride (20 ml.), treated with acetic anhydride (1 ml.) containing perchloric acid (4 drops; 70%) for 15 min. at room temperature, gave *14-methyl-A-norcholest-3(5)-en-3-yl acetate* (XI), m. p. 111—112° (from methanol), $[\alpha]_D$ +86° (*c*, 1·9) (Found: C, 80·85; H, 11·35. $C_{29}H_{48}O_2$ requires C, 81·25; H, 11·3%). This enol acetate (500 mg.) in chloroform (10 ml.) was treated with ethereal perphthalic acid (10 ml.; excess) for 2 hr. at room temperature (uptake of 1 mol. of oxidant), to give *14-methyl-3-oxo-A-norcoprostan-5β-yl acetate* (XIII; R = Ac). Recrystallised from methanol this had m. p. 139—140°, $[\alpha]_D$ +156° (*c*, 2·4), $\lambda_{max.}$ 303 mμ (ε 80) (Found: C, 78·4; H, 10·9. $C_{29}H_{48}O_3$ requires C, 78·3; H, 10·9%). For larger-scale preparation of this compound, the total enol acetylation product was treated with perphthalic acid, to give the ketone acetate in about 60% overall yield.

14-Methyl-A-norcoprostane-3 : 5β-diol (XIV; R = H) *and its Derivatives.*—14-Methyl-3-oxo-A-norcoprostan-5β-yl acetate (see above) (100 mg.) in dry ether (10 ml.) was added to a solution of lithium aluminium hydride (100 mg.) in dry ether (40 ml.) and the mixture refluxed for 3 hr., to give *14-methyl-A-norcoprostane-3 : 5β-diol* (XIV; R = H). Recrystallised as long needles from chloroform–light petroleum (b. p. 40—60°), this had m. p. 188—195°, $[\alpha]_D$ +30° (*c*, 1·15) (Found: C, 80·3; H, 12·1. $C_{27}H_{48}O_2$ requires C, 80·15; H, 11·95%). Treatment with pyridine–acetic anhydride on the steam-bath for 1 hr. and chromatography over alumina with elution by ether containing 1% of methanol gave the *3-monoacetate* (XIV; R = Ac). Recrystallised from aqueous methanol this had m. p. 121—122°, $[\alpha]_D$ +27° (*c*, 1·5) (Found: C, 78·3; H, 11·55. $C_{29}H_{50}O_3$ requires C, 78·0; H, 11·3%).

14-Methyl-A-norcoprostane-3 : 5β-diol (100 mg.) in acetic anhydride (3 ml.) was treated at room temperature with perchloric acid (1 drop; 70%) for 10 min. Filtration in benzene solution through alumina and crystallisation from methanol furnished 14-methyl-A-norcoprostan-3-one (see above), identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +142° (*c*, 1·6)}.

The diol (100 mg.) in "AnalaR" acetic acid (10 ml.) was treated with chromium trioxide (20 mg.) in the same solvent (10 ml.), and the solution left at room temperature for 15 min. Crystallisation of the product from aqueous acetic acid afforded *14-methyl-3-oxo-A-norcoprostan-5β-ol* (XIII; R = H), m. p. 185—187°, $[\alpha]_D$ +135° (*c*, 0·88) (Found: C, 80·35; H, 11·3. $C_{27}H_{46}O_2$ requires C, 80·5; H, 11·5%). This hydroxy-ketone (25 mg.) with acetic anhydride (1 ml.) containing perchloric acid (1 drop; 70%) for 5 min. at room temperature gave 14-methyl-3-oxo-A-norcoprostan-5β-yl acetate (see above), identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +151° (*c*, 1·0)}.

Reduction of Some αβ-Unsaturated Ketones with Lithium and Liquid Ammonia.—Cholest-4-en-3-one (250 mg.) in ether (50 ml.) was added rapidly to an excess of lithium metal in liquid

ammonia (50 ml.), and the mixture stirred for 5 min. Ethereal *tert.*-butanol was added to destroy the excess of lithium. Chromatography of the product over alumina, elution with benzene, and crystallisation from methanol gave cholestanone (155 mg.), identified by m. p., mixed m. p., and rotation $\{[\alpha]_D +42°$ (*c*, 1·6)$\}$.

Similarly stigmasta-4 : 22-dien-3-one (250 mg.) gave stigmast-22-en-3-one (130 mg.), identified by m. p., mixed m. p., and rotation $\{[\alpha]_D +21°$ (*c*, 2·1)$\}$, and ergosta-4 : 22-dien-3-one afforded ergost-22-en-3-one, similarly identified $\{[\alpha]_D +5°$ (*c*, 0·9)$\}$.

We thank the Government Grants Committee of the Royal Society, the Central Research Fund of London University and Imperial Chemical Industries Limited for financial assistance. Two of us (D. A. J. I. and B. R. T.) are indebted to the International Wool Secretariat for (respectively) Predoctorate and Postdoctorate Research Fellowships.

BIRKBECK COLLEGE, LONDON, W.C.1. [*Received, November 14th*, 1953.]

The Conversion of Hecogenin Acetate into 11-Oxotigogenin Acetate.

By J. W. CORNFORTH, J. M. OSBOND, and G. H. PHILLIPPS.

[Reprint Order No. 4811.]

A process is described for replacing the 12-keto-group in hecogenin acetate by an 11-keto- or 11β-hydroxy-group. Translocation of the oxygen atom is effected by formation of an 11β : 12β-epoxide; the reaction of this with hydrogen bromide yields a 12α-bromo-11β-alcohol.

DEOXYCHOLIC ACID was the raw material initially used for partial synthesis of 11-oxygenated steroids, and several elegant procedures have been reported for substituting an oxygen atom at $C_{(11)}$ for the existing one at $C_{(12)}$. The sapogenin hecogenin (3β-hydroxy-5α : 22a-spirostan-12-one) is another readily accessible $C_{(12)}$-substituted steroid: it is a by-product in the manufacture of sisal fibre (Callow, Cornforth, and Spensley, *Chem. and Ind.*, 1951, 699; Spensley, *ibid.*, 1952, 426). The *trans*-relation of rings A and B and the presence of heterocyclic rings E and F limit the application to hecogenin of experience gained with deoxycholic acid. Preferential elimination of the 12-keto-group in an 11 : 12-diketone, discovered in the bile acid series by Wintersteiner and Moore (*J. Biol. Chem.*, 1946, **162**, 725), was applied, with improvements, by Djerassi, Ringold, and Rosenkranz (*J. Amer. Chem. Soc.*, 1951, **73**, 5513) in the preparation of 11-oxo-5α-22a-spirostan-3β-yl acetate (VII) from hecogenin acetate (I). Another conversion of (I) into (VII) is less direct, proceeding by way of a 7 : 9(11)-diene (Hirschmann, Snoddy, and Wendler, *ibid.*, 1953, **75**, 3252).

The present work has already been briefly reported (Cornforth and Osbond, *Chem. and Ind.*, 1953, 919). We are indebted to Dr. A. Wettstein for letting us see in advance of publication a detailed paper (Schmidlin and Wettstein, *Helv. Chim. Acta*, 1953, **36**, 1241) which describes similar experiments. The plan for the work was based on the following considerations:

(1) Hecogenin acetate can be brominated in the 11(presumably the 11α)-position (Djerassi, Martinez, and Rosenkranz, *J. Org. Chem.*, 1951, **16**, 303; Mueller, Stobaugh, and Winniford, *J. Amer. Chem. Soc.*, 1951, **73**, 2400).

(2) The carbonyl group in ω-bromoacetophenone can be reduced by sodium borohydride without loss of halogen (Chaikin and Brown, *ibid.*, 1949, **71**, 122).

(3) Reduction of the 12-keto-group in hecogenin by lithium aluminium hydride gives the 12β-alcohol along with its 12α-epimer (Hirschmann, Snoddy, and Wendler, *ibid.*, 1952, **74**, 2694).

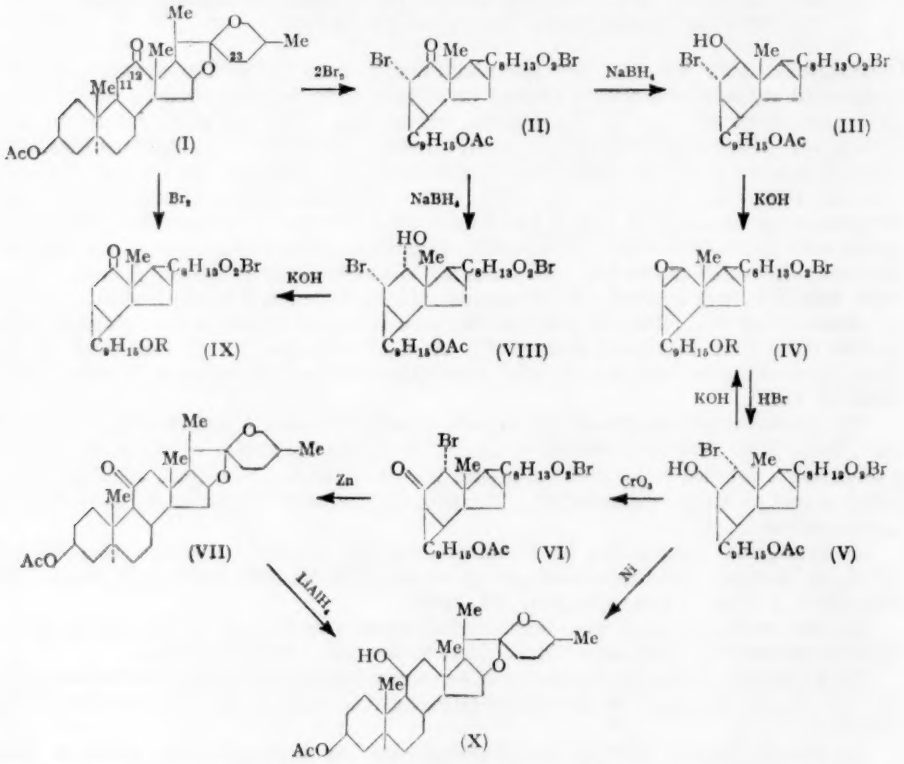
(4) Methyl 3α-acetoxy-11α : 12α-epoxycholanate on hydrogenolysis yields a 12α-alcohol (Press and Reichstein, *Helv. Chim. Acta*, 1942, **25**, 878), whereas the corresponding 11β : 12β-epoxide gives an 11β-alcohol (Ott and Reichstein, *ibid.*, 1943, **26**, 1799). If the difference between these α- and β-epoxides persists in the mode of addition of hydrogen bromide, the 11β : 12β-epoxide should give a 12α-bromo-11β-alcohol, since the 11α : 12α-

epoxide with hydrogen bromide affords an 11β-bromo-12α-alcohol (Gallagher and Long, *J. Biol. Chem.*, **1946**, **162**, 495).

(5) Methyl 3α-acetoxy-12α-bromo-11β-hydroxycholanate (obtained by addition of hypobromous acid to the 11-ene) can be oxidized by chromic acid to the 12α-bromo-11-ketone, which is reduced by zinc to methyl 3α-acetoxy-11-oxocholanate (Ott and Reichstein, *loc. cit.*).

From these analogies it appeared that the transformation (I) ⟶ (II) ⟶ (III) ⟶ (IV) ⟶ (V) ⟶ (VI) ⟶ (VII), shown in the diagrams, would be feasible; and so it proved in practice.

Reduction of 11α : 23ξ-dibromo-12-oxo-5α : 22a-spirostan-3β-yl acetate (II) with sodium borohydride was conveniently carried out in aqueous-alcoholic suspension containing sodium hydrogen carbonate (which inhibits, presumably by buffer action, the formation of bromide ion). The product could be separated by chromatography into two isomeric bromohydrins, 11α : 23ξ-dibromo-12β-hydroxy-5α : 22a-spirostan-3β-yl acetate (III) and 11α : 23ξ-dibromo-12α-hydroxy-5α : 22a-spirostan-3β-yl acetate (VIII), the former (III) predominating. An observation of interest is the reluctance of the 12β-hydroxyl group in (III) to undergo acetylation (see Experimental section). On treatment with cold aqueous-alcoholic alkali the bromohydrin (III) was converted smoothly into 23ξ-bromo-11β : 12β-epoxy-5α : 22a-spirostan-3β-ol (IV; R = H). Under the same conditions, the isomer (VIII) yielded no epoxide, 23ξ-bromo-3β-hydroxy-5α : 22a-spirostan-12-one (23-bromohecogenin) (IX; R = H) being formed in good yield.



When either the 3β-hydroxy-epoxide or its 3-acetate (IV) was treated in acetic acid with hydrogen bromide, 12α : 23ξ-dibromo-11β-hydroxy-5α : 22a-spirostan-3β-yl acetate (V) was formed. The sparing solubility of this compound rendered unnecessary the separation of

the bromohydrins (III) and (VIII) and the purification of the epoxide (IV), for the new bromohydrin (V) could be freed from 23-bromohecogenin acetate (arising from the unwanted isomer VIII) by washing with benzene.

Oxidation of the bromohydrin (V) proceeded smoothly; the resulting 12α : 23ξ-dibromo-11-oxo-5α : 22a-spirostan-3β-yl acetate (VI) was easily reduced by zinc dust in acetic acid–sodium acetate to 11-oxo-5α : 22a-spirostan-3β-yl acetate (11-oxotigogenin acetate) (VII). The properties of this substance were in good agreement with earlier data (Chamberlin *et al.*, *J. Amer. Chem. Soc.*, 1951, **73**, 2396; Djerassi, Ringold, and Rosenkranz, *loc. cit.*).

Reduction of the ketone (VII) with lithium aluminium hydride, followed by acetylation, gave 11β-hydroxy-5α : 22a-spirostan-3β-yl acetate (X) which also had the expected properties (cf. Djerassi, Batres, Velasco, and Rosenkranz, *J. Amer. Chem. Soc.*, 1952, **74**, 1712). The same substance (X) was obtained directly from the bromohydrin (V) and Raney nickel. This conversion (V ⟶ X) is of value in assigning configurations at the 11- and 12-positions to the substances (II), (III), (IV), (V), (VI), and (VIII). It is clear that the 11-hydroxy-group in (V) must be β-oriented. Hence the epoxide (IV) from which (V) originated is the 11β : 12β-epimer. The *trans*-mode of addition of acids to epoxides is well established; thus the 12-bromine atom in (V) and (VI) is 12α.

The bromohydrin (III) from which the β-epoxide (IV) originated is necessarily a 12β-alcohol and its epimer (VIII) is therefore a 12α-alcohol. Finally, Bartlett's work (*ibid.*, 1935, **57**, 224) on the behaviour of *cis*- and *trans*-2-chloro*cyclo*hexanol with alkali—the *cis*-epimer yields a ketone and the *trans* an epoxide—indicates that (III) is a *trans*-bromohydrin and (VIII) a *cis*-bromohydrin, and that the 11-bromine atom in (II), (III), and (VIII) has the expected α-orientation.

An observation from early exploratory work may be added. Reduction of the dibromide (II) by lithium aluminium hydride in ether gave a mixture which, after acetylation, was warmed with zinc in acetic acid. A bromine-containing product was isolated which from its composition and properties appeared to be 23ξ-bromo-5α : 22a-spirost-11-en-3β-yl acetate. Fieser *et al.* (*ibid.*, 1953, **75**, 1700, 1704) have reported similar eliminations from ring A.

Experimental

M. p.s were determined in the Kofler apparatus, and optical rotations in 1% chloroform solution at 20°, except where otherwise stated.

11α : 23ξ-Dibromo-12-oxo-5α : 22a-spirostan-3β-yl Acetate (II).—Hecogenin acetate (10 g.) in chloroform (80 c.c.; ethanol-free) was stirred at 10° during addition of bromine (2·5 c.c.) in chloroform (20 c.c.) during 15 min. After a further 15 min. the pressure in the reaction vessel was reduced to about 30 mm. and the chloroform was distilled through a condenser cooled with solid carbon dioxide. The residue was stirred with a little ethyl acetate until crystallization set in; ethanol (50 c.c.) was then added slowly. The product (7·2 g.) was collected and washed with ethanol; it had m. p. 188—190° and gave 0·98 equivalent of bromide ion on hydrolysis with alcoholic alkali. Recrystallization from chloroform–ethanol gave material, m. p. 189—191° (decomp.), $[\alpha]_D$ −38°, assaying 100% in the same test.

Sodium Borohydride Reduction of the Dibromide (II).—The above dibromide (25 g.), suspended in ethanol (250 c.c.), was stirred during the addition of 7% sodium hydrogen carbonate solution (37·5 c.c.). Sodium borohydride (0·90 g.) in water (12·5 c.c.) was then added and the paste was efficiently stirred for 2½ hr. The product (25·7 g.) was collected after dilution with water (750 c.c.). Assay of the filtrate showed that 0·03 equiv. of bromide ion had been liberated. The crude product (20 g.) in 1 : 1 benzene–light petroleum (40—60°) was chromatographed on alumina (600 g.; acetic acid-washed grade " O," Brockmann II—III).

	Eluates	Volume (ml.)	Residue (g.)	M. p. (decomp.)
I	Benzene–light petroleum 1 : 1	1000	5·50	180°
II	" "	1250	4·20	188
III	" "	1250	1·15	192
IV	Benzene	1250	1·70	192
V	"	1250	0·95	*ca.* 180
VI	"	1250	0·50	*ca.* 180
VII	Ether–benzene 1 : 4	2500	2·70	193

Infra-red analysis showed that fraction I contained unchanged ketone. Fractions II—IV were almost identical; fractions V and VI were essentially the same as II—IV but of lower purity. Fraction VII differed in the " fingerprint " region from II—IV.

Fractions II—IV were combined and crystallized from aqueous acetone, to give 11α : 23ξ-*dibromo*-12β-*hydroxy*-5α : 22*a*-*spirostan*-3β-*yl acetate* (III) as needles, m. p. 197° (decomp.) to 202° (decomp.) according to the rate of heating, $[\alpha]_D$ −56° (Found: C, 55·1; H, 7·0; Br, 25·6. $C_{29}H_{44}O_5Br_2$ requires C, 55·1; H, 7·0; Br, 25·3%). The infra-red spectrum in carbon disulphide showed bands at 3620 (hydroxyl), 1731 and 1238 (acetate); 1010, 944, 914, and 860 (23-bromo-22a-sapogenin); and 724 cm.$^{-1}$ (C–Br).

Fraction VII on crystallization from aqueous methanol gave 11α : 23ξ-*dibromo*-12α-*hydroxy*-5α : 22*a*-*spirostan*-3β-*yl acetate* (VIII), needles, m. p. 198° (decomp.), $[\alpha]_D$ −62° (Found: C, 55·3; H, 7·0; Br, 25·6%). The infra-red spectrum in carbon disulphide showed bands at 3620 (hydroxyl); 1738 and 1242 (acetate); 1016, 948, 917, and 860 (23-bromo-22a-sapogenin) and 723 cm.$^{-1}$ (C–Br). A mixture of the 12α- and the 12β-alcohol melted at *ca.* 190°.

The pure 12β-alcohol (III) could also be separated without chromatography. The crude sodium borohydride reduction product was recrystallized from *iso*propanol, from which it separated in a solvated form, m. p. 128—140°; this product (1 g.) was dissolved in acetic anhydride on a steam-bath, and a few drops of pyridine were added. On cooling, after 1 hr., the 12β-alcohol (III) (0·63 g.) separated, having m. p. 196—201° (decomp.), $[\alpha]_D$ −54° (Found: C, 55·1; H, 7·0%). The infra-red spectrum confirmed that acetylation of the 12β-hydroxyl group had not occurred.

Action of Alkali on the Bromohydrin (III).—The bromohydrin (III) (from chromatography; 500 mg.) and potassium hydroxide (250 mg.) were shaken in ethanol (25 ml.) at room temperature for 4 hr. The resulting solution was left for 20 hr., then concentrated at low pressure and diluted with water; 23ξ-*bromo*-11β : 12β-*epoxy*-5α : 22*a*-*spirostan*-3β-*ol* (IV; R = H) (390 mg.) separated in needles, m. p. 207—209°, $[\alpha]_D$ −26° (Found: C, 63·5; H, 8·1; Br, 15·8. $C_{27}H_{41}O_4Br$ requires C, 63·6; H, 8·1; Br, 15·7%). Infra-red spectrum in Nujol: bands at 3420 (hydroxyl), and 1012, 946, 918, and 868 cm.$^{-1}$ (23-bromo-22a-sapogenin), with only a minute band at 1708 (unconjugated carbonyl). Assay of the aqueous filtrate showed 99% of the theoretical amount of bromide ion. The bromohydrin (III), purified by the acetic anhydride method (above), gave the same epoxide and the infra-red spectrum of the total product showed no carbonyl absorption.

The epoxide (IV; R = H) (300 mg.) was warmed on a steam-bath for 20 min. with acetic anhydride (4 c.c.) and pyridine (4 c.c.). After evaporation at low pressure the residue was triturated with methanol (5 c.c.), giving 23ξ-*bromo*-11β : 12β-*epoxy*-5α : 22*a*-*spirostan*-3β-*yl acetate* (314 mg.), m. p. 233—235°, $[\alpha]_D$ −30°. A sample crystallized from ethanol had m. p. 238—239°, $[\alpha]_D$ −30° (Found: C, 62·8, 63·1; H, 7·9, 7·9; Br, 14·3. $C_{29}H_{43}O_5Br$ requires C, 63·2; H, 7·8; Br, 14·5%). Infra-red spectrum in carbon disulphide: bands at 1735 and 1240 (acetate); 1012, 945, 918, 860 (23-bromo-22a-sapogenin); and 732 cm.$^{-1}$ (C–Br). On hydrolysis the hydroxy-epoxide was regenerated, as felted needles [from light petroleum (b. p. 60—80°)], m. p. 204—206°, $[\alpha]_D$ −28° (Found: C, 63·3; H, 8·1; Br, 15·9%).

Action of Alkali on the Bromohydrin (VIII).—The bromohydrin (VIII) (500 mg.) was treated with alcoholic potassium hydroxide exactly as described for the isomer (III). The crystalline product (400 mg.) had m. p. 206—210° (decomp.) and $[\alpha]_D$ −14°, and gave an acetate, m. p. 225—227°, $[\alpha]_D$ −15°.

For comparison, 23ξ-bromo-12-oxo-5α : 22a-spirostan-3β-yl acetate, prepared by partial debromination of dibromo-compounds, was available, and some of this was converted by methanolysis into the 3β-alcohol which had m. p. 205° (decomp.), $[\alpha]_D$ −14°, after two crystallizations from ethanol (Found: C, 63·6; H, 8·1; Br, 15·6. Calc. for $C_{27}H_{41}O_4Br$: C, 63·6; H, 8·1; Br, 15·7%). Mueller, Stobaugh, and Winniford (*loc. cit.*) gave m. p. 210° (decomp.) and $[\alpha]_D^{26}$ −3° (in dioxan). Mixed m. p.s of this substance, and its acetate, with the corresponding products from the bromohydrin (VIII) were undepressed. The infra-red spectra were also compared and were almost identical: the spectrum of the 3β-alcohol in Nujol showed bands at 3650 (hydroxyl); 1702 (unconjugated carbonyl); 1008, 944, 918, 862 (23-bromo-22a-sapogenin); and 722 cm.$^{-1}$ (C–Br). Spectrum of the acetate in carbon disulphide: bands at 1735 and 1240 (acetate); 1710 (unconjugated carbonyl); 1010, 945, 920, 860 (23-bromo-22a-sapogenin); and 728 cm.$^{-1}$ (C–Br).

12α : 23ξ-*Dibromo*-11β-*hydroxy*-5α : 22*a*-*spirostan*-3β-*yl Acetate* (V).—The following was a general procedure. The acetoxy-epoxide (IV) (5 g.) was ground in a glass mortar with acetic acid (23 c.c.), and hydrogen bromide in acetic acid (2 c.c. of 4·6N) was added dropwise, with

continuous stirring with a pestle, during 10—15 min. After a further 10 min. the crystalline product was collected, washed with acetic acid, dried, and stirred twice on a filter with a little benzene. The residue had m. p. 230—231° (decomp.). When pure acetoxy-epoxide was used the yield was 94% of the theoretical, but it was often convenient to treat the crude sodium borohydride reduction product with alcoholic potassium hydroxide, to acetylate the resulting mixture, and to add hydrogen bromide as above. The contaminating 23-bromohecogenin acetate [arising from the bromohydrin (VIII)] then remained in the acetic acid filtrate and the benzene washings and could be recovered therefrom.

Crystallization of the acetic acid-insoluble product from toluene gave 12α : 23ξ-*dibromo*-11β-*hydroxy*-5α : 22*a*-*spirostan*-3β-*yl acetate* (V) in well-formed needles, m. p. 233—236° (decomp.), $[\alpha]_D$ −23° (Found : C, 55·4; H, 7·2; Br, 25·2. $C_{29}H_{44}O_5Br_2$ requires C, 55·1; H, 7·0; Br, 25·3%). Infra-red spectrum in Nujol : bands at 3560 (hydroxyl); 1717 and 1267 (acetate); 1005, 952, 921, 865 (23-bromo-22a-sapogenin); and 732 cm.$^{-1}$ ($C_{(23)}$–Br).

The same substance (V) separated slowly from a cold solution of the hydroxy-epoxide (IV; R = H) in acetic acid containing hydrogen bromide. When the bromohydrin (V) (315 mg.) was boiled with methanolic potassium hydroxide (10 c.c. of 1%) for 0·5 hr. and the product crystallized from light petroleum (b. p. 60—80°), the hydroxy-epoxide (230 mg.) was obtained, m. p. 202—205°, showing no ketonic absorption in the infra-red.

Oxidation of the Bromohydrin (V).—A solution of 12α : 23ξ-dibromo-11β-hydroxy-5α : 22a-spirostan-3β-yl acetate (600 mg.) in chloroform (10 c.c.; ethanol-free) was shaken with chromium trioxide (0·3 g.) in water (1 c.c.) and acetic acid (4 c.c.) for 1½ hr. at 25°. Water was added; the chloroform layer was shaken with aqueous sodium chloride, then with sodium hydrogen carbonate solution containing sodium chloride, dried ($MgSO_4$) and evaporated. The residue was treated with hot ethyl acetate (3 c.c.). After cooling, the product (448 mg.) was collected; the mother-liquors yielded further crops (total 58 mg.) of identical m. p. and rotation. 12α : 23ξ-*Dibromo*-11-*oxo*-5α : 22*a*-*spirostan*-3β-*yl acetate* (VI) was thus obtained in well-formed prisms, m. p. 229—232° (decomp.), $[\alpha]_D^{24}$ −78° (Found : C, 55·0; H, 6·9; Br, 25·4. $C_{29}H_{42}O_5Br_2$ requires C, 55·2; H, 6·7; Br, 25·3%). Infra-red spectrum in Nujol : bands at 1723 and 1253 (acetate); 1702 (unconjugated carbonyl); 1005, 950, 917, 865 (23-bromo-22a-sapogenin); and 730 cm.$^{-1}$ (C–Br).

11-*Oxo*-5α : 22*a*-*spirostan*-3β-*yl Acetate* (VII).—The dibromo-ketone (VI) (500 mg.) was added to a mixture of zinc powder (2 g.), sodium acetate (1 g.; anhydrous), and acetic acid (5 c.c.). After 1 hour's boiling the product, now halogen-free, was isolated by means of ether. Trituration with methanol gave a nearly pure product (350 mg.), m. p. 215—220° (capillary). Recrystallization from acetone gave pure 11-oxotigogenin acetate (VII), m. p. 229—232°, $[\alpha]_D$ −39° (Found : C, 73·6; H, 9·6. Calc. for $C_{29}H_{44}O_5$: C, 73·7; H, 9·3%). The infra-red spectrum showed the usual acetate, carbonyl, and sapogenin bands. A sample kept for a week with 2 : 4-dinitrophenylhydrazine sulphate in ethanol failed to form a hydrazone; under the same conditions reaction of the hydrazine with hecogenin acetate was complete in a few minutes.

11β-*Hydroxy*-5α : 22*a*-*spirostan*-3β-*yl Acetate* (X).—(i) A concentrated solution of 11-oxotigogenin acetate (VII) in dry ether was treated with lithium aluminium hydride in ether (3 c.c. of 0·21M) and refluxed for 3 hr. Ice and dilute nitric acid were added; the product after recovery from the ether was acetylated with acetic anhydride (0·3 c.c.) and pyridine (0·3 c.c.) on a steam-bath for 0·5 hr. After isolation in the usual way the product was crystallized from acetone. The 11β-hydroxytigogenin acetate separated in rods, m. p. 225—228°, $[\alpha]_D$ −45° (*c* 2 in dioxan) (Found : C, 73·2; H, 9·8. Calc. for $C_{29}H_{46}O_5$: C, 73·4; H 9·7%). The infra-red spectrum showed hydroxy-, acetate, and sapogenin bands; no carbonyl band was detectable.

(ii) 12α : 23ξ-Dibromo-11β-hydroxy-5α : 22a-spirostan-3β-yl acetate (0·75 g.) was added to a refluxing suspension of Raney nickel (~2 g.) in ethyl acetate (30 c.c.). Ethanol (10 c.c.) was then added and heating continued overnight. After removal of catalyst and solvent the product was acetylated with pyridine–acetic anhydride, recovered in the normal manner, and crystallized from acetone. The product (0·1 g.; m. p. 219—225°) was identified by mixed m. p. with the specimen prepared as above; the infra-red spectra of the two samples were identical.

23ξ-*Bromo*-5α : 22*a*-*spirost*-11-*en*-3β-*yl Acetate*.—11α : 23ξ-Dibromo-12-oxo-5α : 22a-spirostan-3β-yl acetate (4·5 g.) was powdered finely, suspended in dry ether (11 c.c.), cooled in ice, and treated with a solution (added all at once) of lithium aluminium hydride in ether (25·5 c.c. of 0·28M). After 0·5 hour's swirling at 0° the mixture was left at 0° overnight and at room temperature for 3 hr.; it was then poured on a mixture of ice and dilute nitric acid. The

product recovered from the ether was dried by being boiled with benzene and was left with pyridine (5 c.c.) and acetic anhydride (10 c.c.) at 37° overnight. After the usual isolation procedure the product was dissolved in acetic acid (10 c.c.), zinc powder (10 g.) was added, and the mixture was warmed for 1 hr. on a steam-bath. Water and chloroform were added; the filtered chloroform extract after being washed with sodium hydrogen carbonate solution was evaporated. The residue was crystallized once from methanol (which yielded 0·97 g. of m. p. 215°), and then from ethyl acetate. *23ξ-Bromo-5α : 22a-spirost-11-en-3β-yl acetate* separated in four-sided tabular crystals, m. p. 226—228° (decomp.), $[\alpha]_D$ −38° (*c* 2 in dioxan) (Found: C, 65·5; H, 8·1. $C_{29}H_{43}O_4Br$ requires C, 65·1; H, 8·0%). This substance was shown to contain bromine and this was not ionized by a boiling solution of sodium in *n*-propanol. The substance gave a yellow colour with tetranitromethane.

NATIONAL INSTITUTE FOR MEDICAL RESEARCH,
THE RIDGEWAY, MILL HILL, LONDON, N.W.7.
GLAXO LABORATORIES LTD., GREENFORD, MIDDX.

[*Received, November 18th*, 1953.]

Reactions of Fluorocarbon Radicals. Part XIII. Alternative Syntheses, Properties, and Spectra of Trifluoro-nitroso- and -nitro-methane.†*

By J. JANDER and R. N. HASZELDINE.

[Reprint Order No. 4733.]

New syntheses for trifluoronitrosomethane, and optimum conditions for the reaction of trifluoroiodomethane with nitric oxide, are described. The nitroso-compound is readily oxidised by oxygen or hydrogen peroxide to give trifluoronitromethane in high yield; improved physical properties are reported. Ultra-violet and infra-red spectra of trifluoronitrosomethane, trifluoronitromethane, and related unsubstituted *C*-nitroso- and *C*-nitro-compounds are discussed, with particular reference to the effect of substitution on the region of characteristic absorption. Comparisons with *O*- and *N*-nitroso- and *O*- and *N*-nitro-compounds show them to be easily distinguished spectroscopically from the *C*-nitroso- and *C*-nitro-compounds.

THE synthesis of a series of polyfluoroalkyl nitroso-compounds was first described in Part X (Haszeldine, *J.*, 1953, 2075; see also *Nature*, 1951, **168**, 1028, and Banus, *ibid.*, 1953, **171**, 4343); alternative and better syntheses are now described for trifluoronitrosomethane and trifluoronitromethane.

Optimum conditions have been derived for the photochemical reaction of trifluoroiodomethane with an excess of nitric oxide in the presence of mercury:

$$CF_3I \xrightarrow{Hg,\ h\nu} CF_3\cdot \xrightarrow{NO} CF_3\cdot NO$$

With a pressure of *ca.* ten atmospheres the yield is high but the conversion is low (20%). The conversion is considerably improved (90%) if the reaction is carried out at atmospheric pressure or below, and for the preparation of small quantities this is the better method. Mercury plays an important rôle by removing iodine and reacting with dinitrogen tetroxide produced as by-product—this tetroxide causes appreciable breakdown and purification becomes difficult. In one experiment where the mercury was not shaken, trifluoronitromethane but not trifluoronitrosomethane was detected amongst the products, *i.e.*:

$$CF_3\cdot + NO_2 \longrightarrow CF_3\cdot NO_2;\ \text{or}\ CF_3\cdot NO \xrightarrow{NO_2} CF_3\cdot NO_2 + \text{decomp.}$$

Trifluoronitrosomethane decomposes at moderate temperatures to give (in glass) silicon tetrafluoride, carbon dioxide, and a small amount of trifluoronitromethane, and the thermal reaction of trifluoroiodomethane with nitric oxide is thus not a suitable preparative method.

Tristrifluoromethylarsine, readily prepared from trifluoroiodomethane and arsenic

* Part XII, Haszeldine, *J.*, 1953, 3761.
† Presented in part at the Amer. Chem. Soc. Meeting, Chicago, Sept. 1953.

(Brandt, Emeléus, and Haszeldine, *J.*, 1952, 2552), yields trifluoronitrosomethane when treated with nitrosyl chloride :

$$As(CF_3)_3 \xrightarrow{NOCl} CF_3{\cdot}NO + AsCl_3$$

The yield is low, since side-reactions, notably the formation of chlorotrifluoromethane, predominate. The photochemical reaction of tristrifluoromethylarsine with nitric oxide also gives low yields of the nitroso-compound.

Trifluoroacetyl iodide, which is a ready source of trifluoromethyl radicals (W. C. Francis, unpublished results), when irradiated in the presence of nitric oxide and mercury, yields trifluoronitrosomethane :

$$CF_3{\cdot}COI \xrightarrow{h\nu,\ Hg} CF_3{\cdot}\dot{C}O \xrightarrow{NO} CF_3{\cdot}NO + CO$$

but the simplest route for the preparation of the *pure* nitroso-compound is still from trifluoroiodomethane; larger quantities of less pure nitroso-compound are best prepared from silver trifluoroacetate (Haszeldine and Jander, *J.*, 1953, 4172).

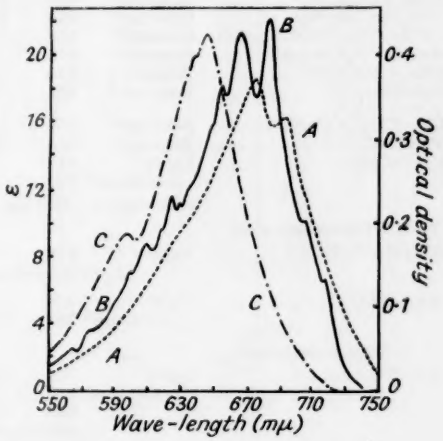


FIG. 1.

A, $CMe_3{\cdot}NO$ in light petroleum. Optical density scale.
B, $CF_3{\cdot}NO$ vapour. ε scale.
C, $CHMeCl{\cdot}NO$ in light petroleum. Optical density scale.

Trifluoronitrosomethane is a blue gas, which is stable in clean glass apparatus, in presence of mercury and in absence of light, and is conveniently purified by utilising its remarkably low melting point (see Experimental part). It condenses to a deep blue liquid at −86·6° (cf. Ruff and Giese's value of −84°; see Haszeldine, *J.*, 1953, 2075), and has a normal Trouton constant of 21·9 which indicates that the compound is not associated; the molecular weight of the gas is normal. There is no evidence for the formation of a dimer of the type $CF_3{\cdot}N(O^-){\cdot}{}^+N(:O){\cdot}CF_3$ (see Part X), and this is supported by spectroscopic examination of trifluoronitrosomethane.

Spectra of Nitroso-compounds.—The ultra-violet spectra of nitroso-compounds are of great theoretical interest. The nitroso-group is electronically similar to oxygen and the monomeric nitroso-compounds are diamagnetic, which suggests that the lowest triplet state is higher than the singlet state. The ultra-violet spectra of trifluoronitrosomethane and related compounds are shown in Table 1. It is very probable that by use of modern photoelectric spectrophotometers the single broad band reported in the earlier literature for nitroso-compounds would be resolved into two or more bands. Monomeric *C*-nitroso-compounds are characterised by a weak absorption band in the region 650—700 mμ. Table 1(*a*) shows that when R in a nitroso-compound R·NO contains only alkyl groups on the α-carbon atom, the absorption is in the region 670—690 mμ, but that when chloro-, phenyl, or nitro-groups are present on the α-carbon atom there is a progressive shift in wave-length to *ca.* 650 mμ. This can be correlated with increase in inductive effect of R with consequent decrease in importance of structures $R{\cdot}{}^+N{-}O^-$ relative to $R{\cdot}N{=}O$ in the excited state. One might

expect that this effect would be at a maximum when R is perfluoroalkyl, but the low-intensity absorption maximum for trifluoronitrosomethane (683 mμ) is considerably shifted relatively to α-chloro-nitroso-compounds, and is more like that for 2-methyl-2-nitroso-

TABLE 1. *Ultra-violet spectra of nitroso-compounds.*

	Solvent	$\lambda_{max.}$ (mμ)	$\varepsilon_{max.}$	$\lambda_{min.}$ (mμ)	$\varepsilon_{min.}$	$\lambda_{max.}$ (mμ)	$\varepsilon_{max.}$	$\lambda_{min.}$ (mμ)	$\varepsilon_{min.}$
(*a*) C-*Nitroso-compounds.*									
CF_3·NO	Vapour [1]	718	6·7	715	6·5	624	12·0	614	8·5
		705	10·5	704	10·0	608	9·0	602	6·5
		683	23·0	676	17·0	600	7·0	580	3·5
		665	21·5	658	17·5	578	4·0	568	2·3
		654	18·5	632	11·0	566	2·5	310—510	<0
		628	11·5	626	11·0	266	20	241	15
Me_3C·NO	Light	692	—	685	—	287	—	266	—
	petroleum [1]	674	—	458—498	—				
	Ether [1]	675	—	440—460	—	296	—	265	—
		Inflection: 686—692 mμ.							
CMe_2Cl·CMe_2·NO	Benzene [2]	690	17·9	—	—	—	—	—	—
CMe_2Br·CMe_2·NO	Benzene [2]	690	17·8	—	—	—	—	—	—
$CHMe_2$·CH_2·CH_2·CMe_2·NO	Benzene [3]	685	—	—	—	—	—	—	—
Me·CO·CH_2·CMe_2·NO	Benzene [4]	670	—	—	—	—	—	—	—
CMe_2·CMeCl·NO	Benzene [2]	670	17·1	—	—	—	—	—	—
O_2N·CMe_2·NO	Benzene [2]	655	21·3	—	—	—	—	—	—
CH_2·$(CH_2)_4$·CCl·NO	Benzene [2]	655	17·9	—	—	—	—	—	—
Ph·CMeCl·NO	Benzene [2]	650	17·0	—	—	—	—	—	—
CHMeCl·NO	Light	648	11·4	604	4·9	319	250	252	26·5
	petroleum [1]	597	5·0	460—468	<0	—	—	—	—
		Inflections: 638 mμ, ε, 10·5; 557 mμ, ε, 1·5							
(*b*) N-*Nitroso-compounds*									
$(CF_2O)(CF_3)$N·NO	Vapour [5]	374	20	320	8·5	—	—	—	—
		Slight inflections: 340—400 mμ							
Me_2N·NO	Light	374	105	369	90	351	98	301	3
	petroleum [5]	361	125	354	94	232	5900	—	—
(*c*) O-*Nitroso-compounds*									
BuO·NO	Light	384·5	33	381·5	31	333	56	326·5	27
	petroleum	370	70	364	49	323	37	318	23
		356	87	349	46	314	27	310·5	24
		344	77	337·5	36	222	1700	—	—
(*d*) *Nitrosyl chloride*									
(Main peaks only)	Vapour	$\lambda_{max.}$, 610, 598·5, 590, 584, 568·5, 562, 547·5, 540·5, 537, 524, 517, 478, 473, 335							

[1] Present work. [2] Hammick and Lister, *J.*, 1937, 489. [3] Anderson, Crumple, and Hammick, *J.*, 1935, 1680. [4] Anderson and Hammick, *J.*, 1935, 30. [5] Jander and Haszeldine, *J.*, 1954, 691, 696.

propane (Fig. 1) or nitrosobenzene. This indicates that structures such as (I), made possible by the tendency for fluorine to participate in hyperconjugation (see *J.*, 1952, 3490; 1953, 922), play an important part.

$$CF_3\cdot NO \longleftrightarrow {}^{-}F\,CF_2{=}\overset{+}{N}{:}O \quad (I); \quad \text{cf. Ph·NO} \longleftrightarrow -\langle\!=\!\rangle{=}\overset{+}{N}{=}O$$

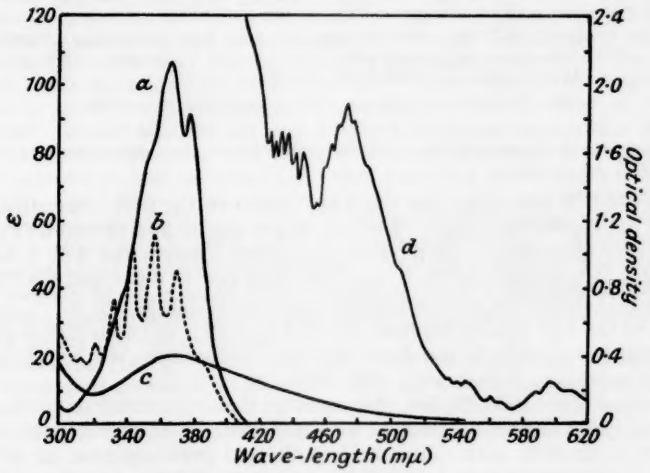
Lewis and Kasha attribute the long wave-length absorption of other *C*-nitroso-compounds to a singlet–triplet transition (*J. Amer. Chem. Soc.*, 1945, **67**, 994), and suggest that, as in oxygen, powerful resonance in the nitroso triplet state involving dipolar forms holds the two atoms closely together and prevents the odd electrons from wandering into R, *i.e.*, R in R·NO is relatively unimportant in determining colour, as is actually found. More recently Orgel (*J.*, 1953, 1276) has suggested that the transition involved is a singlet–singlet σ–π.

The spectrum of trifluoronitrosomethane shows appreciable fine structure in its long wave-length band, which could undoubtedly be resolved further by operating at lower temperatures. The band at lower wave-length (266 mμ) shows no fine structure, and be-

tween the two bands the absorption is extremely weak, so that the position of the minimum could not be determined accurately. The nitroso-compound will clearly be diamagnetic.

The nitroso-group absorption in 2-methyl-2-nitrosopropane is sensitive to solvent changes; in ethyl ether, for example, the long wave-length maximum is unresolved and the position of the short wave-length maximum is shifted by 9 mμ relatively to its position in light petroleum. A marked solvent effect of 15 mμ with loss of fine structure was noted recently for nitrosamines (Haszeldine and Jander, *J.*, 1953, 691). The nitroso-group absorption in these *N*-nitroso-compounds is considerably displaced to shorter wave-length relatively to the corresponding absorption for *C*-nitroso-compounds [Table 1(*b*)]; the weak long wave-length band again shows the characteristic fine structure of the nitroso-group even when fluorine is present in the molecule [*e.g.*, *N*-nitroso-*ON*-bistrifluoromethylhydroxylamine, Table 1(*b*)], and it is very probable that the same fundamental transition as for *C*-nitroso-compounds is involved. The shift to shorter wave-length for the *N*-

FIG. 2.



(*a*) Diethylnitrosamine in light petroleum.
(*b*) Amyl nitrite in light petroleum.
(*c*) *N*-Nitroso-*ON*-bistrifluoromethylhydroxylamine vapour.
(*d*) Nitrosyl chloride vapour. Optical density scale.

nitroso-compounds might be attributed to partial electron transfer in the ground state from the lone pair on nitrogen to the antibonding π orbital.

The nitroso-group in *O*-nitroso-compounds, *e.g.*, nitrites, is much less sensitive to solvent changes (Haszeldine and Jander, *loc. cit.*), and shows absorption similar to that for *N*-nitroso-compounds but with marked resolution of the band [Table 1(*c*)]. The strong absorption at shorter wave-length (220—230 mμ) observed in nitrites and nitrosamines is absent from the spectra of *C*-nitroso-compounds. Finally, when the nitroso-group is attached to an auxochrome such as chlorine ($Cl-N{=}O \longleftrightarrow {}^{+}Cl{=}N-O^{-}$), there is multiple weak absorption in the visible region [Table 1(*d*); see also Goodeve and Katz, *Proc. Roy. Soc.*, 1939, **172**, *A*, 432]. The two main bands at 475 and 595 mμ may be attributed to singlet–singlet or singlet–triplet transitions in the nitroso-group. The nitroso-group absorption is compared in Fig. 2.

The infra-red spectrum of trifluoronitrosomethane is shown in Table 2; the carbon–fluorine absorption produces the broad bands near 8·0 μ, and the stretching vibration of the nitroso-group is clearly at 6·25 μ. The infra-red spectra of other monomeric *C*-nitroso-compounds have not been reported, and measurements have therefore been made on 2-methyl-2-nitrosopropane and nitrosobenzene. Both these compounds exist as colourless

dimers of the type R·N(O–)·$^{+}$N(:O)R in the solid state, but are converted into the blue or green monomers in solution. The spectrum of dimeric 2-methyl-2-nitrosopropane shows strong C–H absorption at 6·8 μ, but only weak bands elsewhere in the 6·0—7·0 μ region; there is a very strong band at 7·34 μ. The monomer is formed in tetrachloroethylene solution and the 7·34 μ band is considerably reduced in intensity; this band is therefore assigned to the N:O vibration in the dimer. The strong C–H band is at 6·8 μ in the spectrum of the solution, and a new strong band appears at 6·46 μ; this band is clearly the N:O stretching vibration in the monomer. The N–O vibration in the dimer can be assigned to the strong band at 7·88 μ or possibly 8·50 μ. An alternative assignment of the above bands (but less likely in view of the intensity changes) is that the N:O vibration in the dimer is at 6·8 μ with the carbon–hydrogen absorption of the *tert.*-butyl group at 7·35 μ.

Nitrosobenzene dimer shows C–H absorption at 6·93 μ and a strong band at 7·19 μ

TABLE 2. *Infra-red spectra.*

CF_2·NO vapour (C.S. 82) *	3·16 (w), 3·60 (w), 4·18 (w), 5·10, 5·17 (w doublet), 5·45 (w), 6·25 (vs), 7·83 (vs), 8·0 (vs), 8·47 (s), 9·73 (m), 10·25 (m), 10·5 (w), 12·35 (m), 13·53, 13·68, 13·86 (s triplet).
CF_2·NO_2 vapour (C.S. 83)	3·39 (w), 3·70 (w), 4·10 (w), 5·66 (w), 6·13, 6·17 (vs doublet), 7·31 (m), 7·64, 7·78, 7·87 (vs triplet), 8·59, 8·64, 8·69, 8·73 (vs quadruplet), 10·0 (w), 11·50, 11·62, 11·72 (s triplet), 13·20, 13·33, 13·44 (vs triplet).

m = medium, s = strong, vs = very strong, w = weak.

* Spectra thus marked have been deposited with the Chemical Society. Photocopies, price 3*s.* 0*d.* per copy per spectrum, post free, may be obtained from the General Secretary on application quoting the C.S. no.

attributed to the N:O vibration; the last band cannot be the C–H absorption, since nitrobenzene does not have a band here. Medium bands appear at 6·63 and 6·72 μ, and one of these is the ring absorption. In tetrachloroethylene solution the 6·63 μ band (now at 6·61 μ) becomes very strong relative to the C–H band now at 6·9 μ, and the 7·2 μ band disappears; the N:O stretching vibration in the monomer is thus at 6·61 μ.

The shift of the N:O absorption from 6·5—6·6 to 6·25 μ when fluorine is present in the molecule parallels the shift in the band for nitro-compounds (see below) and carbonyl compounds (Haszeldine, *Nature*, 1951, **168**, 1028).

Ruff and Giese (*Ber.*, 1936, **69**, 598, 684) reported that trifluoronitrosomethane could not be oxidised (*e.g.*, that there is no reaction with 60% nitric acid after 3 hours, with chromic anhydride in acetic acid, with Caro's acid, with acid permanganate, or with hydrogen peroxide), but in an earlier paper (Haszeldine, *J.*, 1953, 2075) it was shown that vigorous oxidising agents yielded trifluoronitromethane. Yields were low and there was appreciable decomposition. In the same paper the preparation of 1-chloro-2-nitrotetrafluoroethane by reaction of nitrosyl chloride with tetrafluoroethylene under mild conditions was reported, and it follows that oxidation of the nitroso-group (formed initially) to the nitro-group must have occurred readily. In accord with this deduction, it has now been found that trifluoronitromethane can be prepared in high yield (80%) by reaction of the nitroso-compound with oxygen at 100° or with hydrogen peroxide at 50°. The nitro-compound can now be readily purified, and the boiling point originally reported (Haszeldine, *loc. cit.*) is corrected to −31·1°; the nitro-compound has a normal Trouton constant.

Spectra of Trifluoronitromethane.—The ultra-violet absorption spectrum of trifluoronitromethane ($\lambda_{max.}$ 279, ε 11·0; $\lambda_{min.}$ 239, ε 2·0) resembles that of other alkyl and halogenoalkyl nitro-compounds (cf. *J.*, 1953, 2525), but the intensity of absorption is lower than that for trichloronitromethane. *N*-Nitro-compounds show much more powerful absorption than *C*-nitro-compounds, but at a lower wave-length (*e.g.*, Me_2N·NO_2 in dioxan, $\lambda_{max.}$ 240 mμ, ε 6300). Nitrates, as representative *O*-nitro-compounds, show a low-intensity inflection at *ca.* 260 mμ and thus have general resemblance to *C*-nitro-compounds, but differ considerably from *N*-nitro-compounds. The reverse is true for *O*-, *C*-, and *N*-nitroso-compounds (see above). The importance of resonance of the type X–N=O ⟷ $^{+}$X=N–O^{-} (X = N, O, or Cl) on the absorption spectra of compounds containing nitrogen and oxygen has been emphasised earlier (Haszeldine and Jander, *J.*, 1953, 691), and is again shown by the marked difference in spectra of trifluoro-nitroso- and -nitro-methane.

The infra-red spectrum of trifluoronitromethane (Table 2) shows the asymmetric stretching vibration as a doublet at 6·13, 6·17 μ; tetranitromethane similarly shows a doublet for this band (6·08, 6·19 μ). The symmetric stretching vibration appears as a triplet at 7·64, 7·78, 7·87 μ, and the carbon–fluorine stretching vibration bands are centred on 8·7 μ. The spectrum of trifluoronitromethane supports the assignments made for 1-chloro-2-nitrotetrafluoroethane (*J.*, 1953, 2525), and again shows that the asymmetric and the symmetric band of the nitro-group move to shorter and longer wave-length respectively as the inductive effect of R in $R{\cdot}NO_2$ increases. The C–N vibration in trifluoronitromethane is assigned to the 11·6 μ triplet, and in trifluoronitrosomethane to the 12·35 μ band (cf. $CBr_3{\cdot}NO_2$ 11·9 μ, $CCl_3{\cdot}NO_2$ 11·9 μ, $CClF_2{\cdot}CF_2{\cdot}NO_2$ 11·0 μ); both compounds show the very characteristic well-resolved triplet assigned to the CF_3 deformation (13·20, 13·33, 13·44 μ; 13·53, 13·68, 13·86 μ respectively).

Experimental

Trifluoroiodomethane (*J.*, 1951, 584) was purified and stored *in vacuo*. Nitric oxide, prepared from potassium nitrite, potassium iodide, and sulphuric acid, was passed over calcium chloride, phosphoric anhydride, and soda-lime, and purified by distillation *in vacuo* (Found: *M*, 30·5. Calc. for NO: *M*, 30). Tristrifluoromethylarsine was prepared as described earlier (*J.*, 1952, 2552). Reactions were carried out in sealed silica or Pyrex tubes with the careful exclusion of air or moisture. A Hanovia lamp was used, without the filter, as the source of ultra-violet light.

Reaction of Trifluoroiodomethane with Nitric Oxide.—(a) *Thermal.* Trifluoroiodomethane (1·3 g.), nitric oxide (0·4 g.), and mercury (5 ml.) were sealed in a 50-ml. Pyrex tube and heated in the dark at 100—140° (4 days), then 160° (12 hr.). A yellow solid was deposited on the walls of the vessel, and a blue gas could be seen. A small amount of non-condensable gas was removed, and the volatile products were fractionated to give unchanged trifluoroiodomethane (*ca.* 50%) and a blue gas contaminated with carbon dioxide. The last compound was removed by its preferential absorption by 5% aqueous sodium hydroxide when shaken together for 2—3 min. Further distillation gave trifluoronitrosomethane (3%; 6% based on trifluoroiodomethane used), identified by its infra-red spectrum.

Trifluoroiodomethane (13·9 g.), nitric oxide (4 g.), and mercury (10 ml.), heated to 160° for 6 days in a 100-ml. steel autoclave which was rocked, gave unchanged trifluoroiodomethane, nitric oxide, carbon dioxide, and probably carbonyl fluoride as the only reaction products. After 4 days at 180°, then 2 days at 200°, a similar reaction mixture gave only decomposition products.

In a control experiment trifluoronitrosomethane (0·030 g.) was sealed in a 30-ml. Pyrex tube and heated at 100° (12 hr.), then 145° (24 hr.), without change. After 12 hr. at 160° there was a slight fading of colour, and after 84 hr. at 170° the colour had completely disappeared. The gaseous products were silicon tetrafluoride (mainly), trifluoronitromethane (trace), carbon dioxide, and carbonyl fluoride. A small quantity of a white, water-soluble, crystalline inorganic solid was also formed.

(b) *Photochemical, at greater than atmospheric pressure.* In a typical experiment, trifluoroiodomethane (5·5 g., 0·028 mole), nitric oxide (1·7 g., 0·057 mole), and mercury (15 ml.) were sealed in a 250-ml. silica tube which was fitted with an open-frame heater so that it could be heated and exposed to light. The horizontal tube was shaken vigorously in a vibro-shaker so that the mercury was intimately mixed with the vapour and liquid; this is essential for efficient reaction. The tube was heated to 110° and exposed to ultra-violet light for 7 days. Use of higher temperatures, or longer periods of irradiation, failed to increase the yield substantially. The products from six reaction tubes were combined and distilled *in vacuo* to remove unchanged trifluoroiodomethane (60—80%). The more volatile fraction was mixed with an equal volume of oxygen and kept in the dark for 1 hr. to convert nitric oxide into dinitrogen tetroxide, which was removed by distillation. The almost pure nitroso-compound was finally purified by being shaken with 5% aqueous sodium hydroxide for 10 min. to remove traces of carbon dioxide, etc., and was then redistilled.

An alternative and often more convenient method of purification was as follows: After removal of the excess of nitric oxide as above, the crude nitroso-compound was passed slowly down a vertical glass tube (7 mm., internal diameter) which was cooled on the outside over a 6—8 cm. length by liquid nitrogen in a Dewar vessel. The vertical glass tube passed through the base of the Dewar vessel and was connected by a vacuum-tap to a receiver (50 ml. capacity)

which was independently cooled in liquid nitrogen. Under these conditions trifluoronitrosomethane condensed to a blue viscous liquid which flowed down the glass tube, through the tap, and was collected in the receiver; the impurities (carbon dioxide, silicon tetrafluoride, carbonyl fluoride, and traces of trifluoroiodomethane) are solids at −196°, and collected in the tube. The tap was closed, and the purified trifluoronitrosomethane was transferred to a vacuum-system; the process was usually repeated twice to give spectroscopically pure material, containing at most 0·2% of trifluoroiodomethane.

Both methods of purification gave trifluoronitrosomethane in 20% yield based on trifluoroiodomethane taken (*ca.* 80% on trifluoroiodomethane used). The purity was checked by the molecular weight (Found: *M*, 99. Calc. for $CONF_3$: *M*, 99), by spectroscopic examination, or by vapour-pressure measurements. The vapour pressure of trifluoronitrosomethane, measured over the temperature range −99° to −132°, is represented by the equation $\log_{10} p$ (mm.) = 7·674 − 895·86/*T*, where *T* is the temperature (K). The b. p. is calculated as −86·6°, the latent heat of vaporisation as 4095 cals./mole, and Trouton's constant as 21·9. Ruff and Giese (*loc. cit.*) reported b. p. −84° for an impure sample (vapour pressure 272 mm. at −99·8°. Calc. from above equation: 347 mm.).

(c) *Photochemical, at less than atmospheric pressure.* A 200-ml. silica tube containing mercury (2 ml.) was filled with a 1 : 1·2 molar ratio of trifluoroiodomethane and nitric oxide to a pressure of 700 mm., and was shaken vigorously whilst exposed to ultra-violet light. Instantaneous reaction with formation of mercuric iodide was apparent, and after 8 hr. the reaction products were treated as above and distilled, to give trifluoronitrosomethane (89%), identified spectroscopically, and unchanged trifluoroiodomethane (6%) and nitric oxide; only small amounts of carbon dioxide and breakdown products were noted.

In similar experiments with total initial pressures of 510, 363, and 109 mm., the yields of trifluoronitrosomethane were 79, 83, and 84%, respectively, with a reaction time of 6 hr. The only disadvantage of this method of preparation is the small amount of trifluoroiodomethane which can be used per experiment in equipment of normal size.

(d) *Formation of trifluoronitromethane.* Trifluoroiodomethane (6·5 g.), nitric oxide (2·0 g.), and mercury (15 ml.) were sealed in a 275-ml. silica tube, heated to 100°, shaken, and irradiated for 4 days. The formation of the nitroso-compound was apparent from the blue colour. The shaking was stopped and the ultra-violet lamp was moved near to the tube. After 2 days the blue colour had disappeared and fractionation gave a non-condensible gas, carbon dioxide, unchanged trifluoroiodomethane, an unidentified product, and trifluoronitromethane (*ca.* 25%), identified by its infra-red spectrum.

Reaction of Tristrifluoromethylarsine with Nitrosyl Chloride and with Nitric Oxide.—Tristrifluoromethylarsine (1·0 g.) and nitrosyl chloride (0·65 g.) were heated in a 50-ml. Pyrex tube at 100° for 2 hr. The products were distilled *in vacuo* through a trap cooled to −140° and the more volatile fraction was shaken with 2% aqueous sodium hydroxide solution (3 min.), then redistilled to give a mixture (0·16 g.) of trifluoronitrosomethane and chlorotrifluoromethane, identified by their infra-red spectra. The yield of the nitroso-compound was *ca.* 2%.

In a second experiment tristrifluoromethylarsine (3·3 g.) and nitrosyl chloride (2·2 g.) were heated from 0° to 200° at atmospheric pressure in a flask connected *via* a reflux condenser at −78° to a trap cooled in liquid nitrogen, so that trifluoronitrosomethane could escape from the reaction mixture as soon as formed. Only small amounts of the nitroso-compound were detected.

An experiment in which tristrifluoromethylarsine and nitrosyl chloride were mixed with mercury in a silica tube and exposed to ultra-violet light failed to yield more than traces of trifluoronitrosomethane.

Tristrifluoromethylarsine (2·0 g.), nitric oxide (0·9 g.), and mercury (10 ml.) were sealed in a 180-ml. silica tube which was vigorously shaken and exposed to ultra-violet light for 5 days. After a preliminary purification of the products in a vacuum-system, the mixture of nitric oxide and nitroso-compound was treated as described above, to give trifluoronitrosomethane (0·085 g., 4%) (Found: *M*, 96), identified by its infra-red spectrum.

Trifluoronitrosomethane from Trifluoroacetyl Iodide.—The iodo-compound (4·5 g.), nitric oxide (1·3 g.), and mercury (10 ml.), sealed in a 180-ml. silica tube, heated (100°), shaken, and irradiated for 4 days, gave mercuric iodide, carbon monoxide, carbon dioxide, an unidentified mercurial, and trifluoronitrosomethane (4%).

Trifluoronitromethane.—In a typical experiment trifluoronitrosomethane (0·100 g.) was sealed with oxygen (700 mm. pressure) in a 40-ml. Pyrex tube and heated at 100° until the blue colour disappeared (*ca.* 10 days). The contents of the tube were pumped slowly through a series of

traps cooled in liquid oxygen, and the condensed material was distilled *in vacuo*, to give unchanged trifluoronitrosomethane (0·010 g.), small amounts of decomposition products, and trifluoronitromethane (0·090 g., 78%), b. p. −31·1° (Found: C, 10·5; N, 11·9%; *M*, 115. Calc. for CO_2NF_3: C, 10·4; N, 12·2%; *M*, 115). The infra-red spectrum, b. p., and molecular weight were unchanged after treatment of the nitro-compound with ice-cold 2% aqueous sodium hydroxide for 2 min.

The following vapour pressures have been recorded:

p (mm.)	649·3	673·2	703·2	718·2	735·2	742·2	749·2	758·2	767·2	782·2
Temp. (° c)	−34·4	−33·6	−32·7	−32·3	−31·9	−31·6	−31·5	−31·1	−30·9	−30·5

whence the vapour pressure equation for this limited range is $\log_{10} p$ (mm.) = 7·541 − 1128·3/*T*, where *T* = temperature (K). The b. p. is calculated as −31·1°, the latent heat of vaporisation as 5160 cals./mole, and Trouton's constant as 21·3. Haszeldine (*J.*, 1953, 2075) reported b. p. −21° for a sample prepared by vigorous oxidation of trifluoronitrosomethane. The yield of the nitro-compound by the earlier procedure was low and the difference in b. p. (recorded in an isoteniscope) is caused by impurity in the earlier specimen.

An alternative simple method of oxidation of trifluoronitrosomethane involves hydrogen peroxide. The nitroso-compound (0·9 g.) and a 50% excess of 30% hydrogen peroxide were heated in a sealed tube for 4 days. The blue colour had then disappeared, and distillation *in vacuo* gave trifluoronitromethane (76%), identified spectroscopically, and a small amount of carbon dioxide; the aqueous solution gave a positive test for fluoride ion.

Spectra.—A Unicam Spectrophotometer and a Perkin-Elmer 21 Double Beam Spectrophotometer were used. The latter had rock-salt optics. The molar extinction coefficient for vapours is given by $\varepsilon = 760D \times 22{\cdot}4 \times 290/273pl$, where *D* = optical density, *p* = gas pressure (mm.), and *l* = cell length (cm.).

The authors are indebted to Mr. F. E. G. Smith for the preparation of samples of nitrosobenzene and 2-methyl-2-nitrosopropane, and to Imperial Chemical Industries Limited for a sample of pure nitrosyl chloride used in the spectroscopic work. One of them (J. J.) is indebted to Professor H. J. Emeléus for personal assistance, and to the British Council for a British Council Scholarship for Germany during the tenure of which this work was carried out.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, October 16th* 1953.]

Reactions of Fluorocarbon Radicals. Part XIV. Hexafluoroazoxymethane.†*

By J. JANDER and R. N. HASZELDINE.

[Reprint Order No. 4753.]

Reaction of trifluoronitrosomethane with active carbon or with aqueous sodium hydroxide yields hexafluoroazoxymethane and trifluoronitromethane. Ruff and Giese's claim to have prepared trifluoroformamide from trifluoronitrosomethane is disputed. Ultra-violet and infra-red spectroscopic properties of hexafluoroazoxymethane are presented and discussed. The characteristic wave-lengths in the infra-red for compounds containing nitrogen and oxygen can be used diagnostically for fluorine compounds with only slight change.

RUFF and GIESE (*Ber.*, 1936, **69**, 598, 684) obtained impure trifluoronitrosomethane from silver cyanide and fluorine and concluded that the impurity was the colourless, very stable trifluoroformamide, into which the nitroso-compound could be isomerised almost quantitatively by treatment with a variety of reagents including sodium hydroxide and active carbon:

$$CF_3{\cdot}NO \text{ (b. p. } -84°) \longrightarrow F{\cdot}CO{\cdot}NF_2 \text{ (b. p. } -82{\cdot}4°)$$

This reaction would be novel in the chemistry of fluorine compounds since (*a*) it involves the quantitative transfer of fluorine from carbon to nitrogen, and (*b*) the product, which is essentially a derivative of carbonyl fluoride, *i.e.*, an acyl fluoride, is reported to be stable to

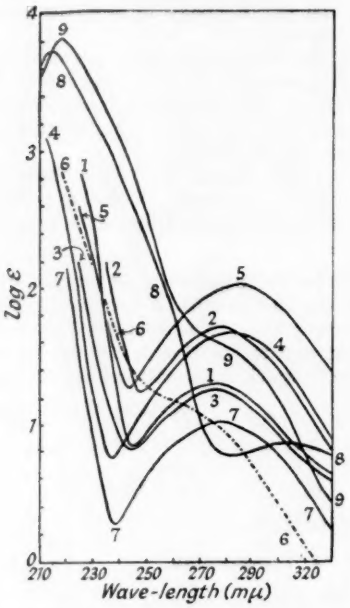
* Part XIII, preceding paper.

† Presented at the meeting of the American Chemical Society in Chicago, Sept. 1953.

heat, acids, water, and alkali. Re-investigation of the reactions of trifluoronitrosomethane gives results which contradict those of Ruff and Giese.

Pure trifluoronitrosomethane, prepared by the reaction of trifluoroiodomethane with nitric oxide (Haszeldine, *J.*, 1953, 2075; Jander and Haszeldine, *loc. cit.*), is slowly decolorised when heated with active charcoal, and yields a colourless compound $C_2ON_2F_6$ of molecular weight 182 (cf. $F{\cdot}CO{\cdot}NF_2$: *M*, 99) and b. p. 7°, trifluoronitromethane (Haszeldine, *loc. cit.*), and (by decomposition in silica apparatus) carbon dioxide and silicon tetrafluoride. The colourless compound, which shows a normal Trouton constant, could be (I), (II), or (III), and (III) can be eliminated on grounds of colour, since nitrosamines are yellow (Haszeldine and Jander, *J.*, 1954, 691). Distinction between (I) and (II) is made in favour of (I) on spectroscopic grounds.

Hexafluoroazoxymethane (I) shows a weak long-wave-length and a very powerful



1, $CH_3{\cdot}NO_2$ *in light petroleum.*
2, $CCl_3{\cdot}NO_2$ *in light petroleum.*
3, $CCl_3{\cdot}NO_2$ *vapour.*
4, $CClF_2{\cdot}CF_2{\cdot}NO_2$ *vapour.*
5, $CClF_2{\cdot}CF_2{\cdot}NO_2$ *in light petroleum.*
6, $EtO{\cdot}NO_2$ *in light petroleum.*
7, $CF_3{\cdot}NO_2$ *vapour.*
8, $CF_3{\cdot}N{:}^{+}N{\cdot}CF_3$ (O⁻) *vapour.*
9, $CH_3{\cdot}N{:}^{+}N{\cdot}CH_2$ (O⁻) *vapour.*

short-wave-length maximum ($\lambda_{max.}$ 303, ε 17·4; $\lambda_{max.}$ 211, ε 8000; $\lambda_{min.}$ 280, ε 6·0) and thus shows a marked resemblance to azoxymethane (Figure, curve 9) and other azoxyalkanes; these show a weak but marked inflection in the 270—290 mμ region (see Langley, Lythgoe,

$CF_3{\cdot}\overset{+}{N}{:}N{\cdot}CF_3$ (O⁻) (I) $\quad CF_3{\cdot}O{\cdot}N{:}N{\cdot}CF_3$ (II) $\quad (CF_3)_2N{\cdot}NO$ (III)

and Rayner, *J.*, 1952, 4191) instead of the 303 mμ maximum in the fluorine compound. Comparison with other compounds containing nitrogen and oxygen is made in the Figure. Definite distinction cannot be made between (I) and (II) on the basis of ultra-violet spectroscopy however, since detailed studies on azo-ethers have not been reported, although it is known that the compound $Ph{\cdot}N{:}N{\cdot}OMe$ is colourless (Bamberger, *Ber.*, 1895, **28**, 225) and that hyponitrous acid has $\lambda_{max.}$ 244 mμ, ε 3550, inflection 294 mμ, ε 25, in 0·1N-sodium hydroxide, and has inflection 244 mμ, ε 80, in 0·1N-hydrochloric acid (Kortüm and Finckh, *Z. physikal. Chem.*, 1940, *B*, **48**, 32).

The infra-red spectrum of the compound $C_2ON_2F_6$ clearly shows it to be (I) and not (II); an azoxy-group, electronically similar to a *C*-nitro-group, shows asymmetric and symmetric stretching vibrations, and these characteristic bands are at 6·37 and 7·80, 7·94 μ for hexafluoroazoxymethane, *i.e.*, shifted to shorter and longer wave-length respectively

relative to the corresponding bands in azoxymethane (Table; Langley *et al., loc. cit.*; cf. $CF_3{\cdot}NO_2$ and $Me{\cdot}NO_2$ in the Table). The nitrogen–oxygen vibration in the infra-red varies in a characteristic manner depending on whether the oxygen is in a nitroso-, nitro-, or azoxy-group, and whether the nitrogen atom is attached to carbon, nitrogen, oxygen, or halogen. The characteristic wave-lengths are shown in the Table, and it is evident that the wave-lengths established for compounds unsubstituted by fluorine can be used diagnostically, with only slight change, for the corresponding fluorine compounds.

Both trifluoronitromethane and hexafluoroazoxymethane are formed when trifluoronitrosomethane is heated with carbon:

$$3CF_3{\cdot}NO \longrightarrow CF_3{\cdot}{}^{+}N(O^{-}){:}N{\cdot}CF_3 + CF_3{\cdot}NO_2$$

although breakdown of trifluoromethyl groups is an important side-reaction. The azoxy-compound boils some 90° below azoxymethane (cf. $Me{\cdot}NO_2$, b. p. 101°, $CF_3{\cdot}NO_2$, b. p. −31°), again revealing the marked influence of fluorine-substitution on boiling point. Although stable to water, aqueous base or acid, and at moderate temperatures, hexafluoroazoxymethane does not show the stability attributed by Ruff to the products from trifluoronitrosomethane, and it seems very probable that "trifluoroformamide" was actually hexafluoroethane or fully fluorinated methylamine ($CF_3{\cdot}NF_2$) produced during the fluorination; these colourless compounds boil close to trifluoronitrosomethane, and are thermally and chemically extremely stable.

Ruff and Giese reported that with 8% aqueous sodium hydroxide trifluoronitrosomethane was converted almost quantitatively (42·1 ml. of gas ⟶ 40·6 ml.) into the alkali-stable trifluoroformamide. With pure trifluoronitrosomethane completely different results are now reported. The blue colour rapidly fades when the nitroso-compound is shaken with aqueous base, and there is immediate formation of fluoride with decrease in the

Characteristic vibrations of compounds containing nitrogen and oxygen.

(a) *Nitroso-compounds.*

C–NO monomers		N–NO		O–NO		X–NO	
$Me_2C{\cdot}NO$	6·46 μ	$R_2N{\cdot}NO$	7·10—7·40 (N:O) 9·15—9·55 (N–O)	$RO{\cdot}NO$	5·76, 6·07, 6·23 triplet * (N:O)	NOCl	5·50, 5·60 doublet
$Ph{\cdot}NO$	6·61	$(CF_3O)(CF_2)N{\cdot}NO$	7·62 (N:O) 9·35 (N–O)		12·5 (N·O)	NOBr	5·55
$CF_3{\cdot}NO$	6·25					NOF	5·42

* Rotational isomerism.

(b) *Nitro-compounds.*

C–NO_2			N–NO_2		O–NO_2	
$Me{\cdot}NO_2$	6·38 (as.)	7·25 (sym.)	$R_2N{\cdot}NO_2$	6·1–6·5 (as.) 7·2–8·0 (sym.)	$RO{\cdot}NO_2$	6·12 (as.) 7·80 (sym.)
$CBr_3{\cdot}NO_2$	6·28 (as.)	7·66 (sym.)				
$CCl_3{\cdot}NO_2$	6·21 (as.)	7·65 (sym.)				
$CClF_2{\cdot}CF_2{\cdot}NO_2$	6·18 (as.)	7·85 (sym.)	R = alky			
$CF_3{\cdot}NO_2$	6·13, 6·17 doublet (as.)	7·64, 7·78, 7·87 triplet (sym.)				

(c) *Azoxy-compounds.*

$CH_3{\cdot}\overset{+}{N}(O^{-}){:}N{\cdot}CH_3$	6·55 (as.)	7·45 (sym.)	$CF_3{\cdot}\overset{+}{N}(O^{-}){:}N{\cdot}CF_3$	6·37 (as.) 7·80, 7·94 doublet (sym.)	
$R{\cdot}\overset{+}{N}(O^{-}){:}N{\cdot}R$	6·6–6·7 (as.)	7·6–7·8 (sym.)			

amount of gaseous material. The reaction has been followed by infra-red spectroscopic examination: trifluoronitromethane and hexafluoroazoxymethane are the only gaseous products, and there is no product which corresponds to trifluoroformamide; prolonged alkali-treatment completely destroys the gaseous material. Trifluoronitromethane is known to be unstable to aqueous alkali; the azoxy-compound is stable unless shaken with the base. A reaction similar to that observed by Bamberger for nitrosobenzene (*Ber.*, 1900, **33**, 1939) thus occurs, at least in part:

$$3CF_3{\cdot}NO \longrightarrow CF_3{\cdot}NO_2 + CF_3{\cdot}{}^{+}N(O^{-}){:}N{\cdot}CF_3;\ \text{cf. } 3Ph{\cdot}NO \longrightarrow Ph{\cdot}NO_2 + Ph{\cdot}{}^{+}N(O^{-}){:}NPh$$

A possible reaction scheme is formation in solution of an ion such as $CF_3 \cdot {}^{+}NH(O^{-}) \cdot OH$ which, by reduction of the nitroso-compound, yields the hydroxylamine, $CF_3 \cdot NH \cdot OH$, and trifluoronitromethane. The decomposition of the hydroxylamine into fluoride and carbonate would be consistent with the known properties of compounds containing the $-CF_2 \cdot NH-$ groups; the competitive reaction with trifluoronitrosomethane would yield hexafluoroazoxymethane.

It must thus be concluded that trifluoronitrosomethane can be converted into hexafluoroazoxymethane and trifluoronitromethane, but not into trifluoroformamide; this compound has yet to be prepared.

Experimental

Trifluoronitrosomethane was prepared from trifluoroiodomethane and nitric oxide by the method described earlier (*J.*, 1953, 2075, preceding paper); its purity was tested by infra-red spectroscopic examination.

Hexafluoroazoxymethane.—In a typical experiment trifluoronitrosomethane (0·300 g.) was sealed in a 50-ml. silica tube with decolorising charcoal (1·5 g.) which had been activated *in vacuo* at 150° for 1 hr. Only a pale blue colour was apparent at room temperature and this disappeared after the tube had been heated at 100° for 48 hr. The products (0·24 g.), removed by pumping for 1 hr. with the tube heated at 100°, were distilled in a vacuum, to give trifluoronitromethane (0·025 g., 7%), identified by its infra-red spectrum, carbon dioxide, silicon tetrafluoride, etc. (0·085 g.), and ***hexafluoroazoxymethane*** (0·130 g., 47%), b. p. 6·9° (Found: C, 13·5; N, 15·8; F, 61·7%; *M*, 182. $C_2ON_2F_6$ requires C, 13·2; N, 15·4; F, 62·6%; *M*, 182).

The following vapour pressures were recorded for hexafluoroazoxymethane:

p (mm.)	609·1	663·1	699·5	716·0	742·5	750·5	763·0	771·5
Temp. (°c)	1·6	3·6	4·9	5·4	6·4	6·6	7·0	7·3

whence the vapour pressure equation is $\log_{10} p$ (mm.) $= 7{\cdot}886 - 1407{\cdot}0/T$ (T = temp., °K), the b. p. is calculated as 6·9°, the latent heat of vaporisation is 6410 cals./mole, and Trouton's constant is 22·9.

Hexafluoroazoxymethane is stable to water, 10% hydrochloric acid, or 10% aqueous sodium hydroxide at 20° during 20 days.

Reaction of Trifluoronitrosomethane with Aqueous Sodium Hydroxide.—The nitroso-compound (0·050 g.), shaken with 10% aqueous sodium hydroxide (15 ml.) for 12 hr. in a sealed 50-ml. Pyrex tube, was completely destroyed. The product (0·030 g.) (Found: *M*, 129. Calc. for CO_2NF_3: *M*, 115. Calc. for $C_2ON_2F_6$: *M*, 182) was shown by infra-red spectroscopic examination to be trifluoronitromethane (80%), and hexafluoroazoxymethane (20%).

In a second experiment trifluoronitrosomethane (0·030 g.) was sealed in a 25-ml. Pyrex tube with 7·5% aqueous sodium hydroxide (4·5 ml.) and shaken for 25 min. The infra-red spectrum of the residual volatile material (0·016 g.) revealed trifluoronitrosomethane, trifluoronitromethane, and hexafluoroazoxymethane in an approximate ratio 1 : 6 : 3. The mixture was resealed in the same reaction vessel and was shaken for a further 20 min. Spectroscopic examination of the product (0·003 g.) showed trifluoronitrosomethane, trifluoronitromethane, and hexafluoroazoxymethane in an approximate ratio 1 : 70 : 35. The product, resealed and shaken for 85 min., gave only trifluoronitromethane and hexafluoroazoxymethane (0·001 g.) in a ratio of 2 : 1. Qualitative tests on the aqueous solution for fluoride and nitrite (or nitrate) were positive.

Spectra.—A Unicam Spectrophotometer and Perkin-Elmer Model 21 Double Beam Spectrophotometer were used. The infra-red spectra of hexafluoroazoxymethane and ethyl nitrate are recorded in the annexed Table.

Infra-red spectra.

$CF_3 \cdot N{:}^{+}N(O^{-}) \cdot CF_3$ (C.S. 84*) Main bands	6·37 (vs), 6·65 (w), 7·07 (w), 7·36 (m), 7·57 (s), 7·80 (vs), 7·94 (vs), 8·23 (s), 8·50 (vs), 8·64 (vs), 9·00 (s), 9·83 (w), 10·67 (vs), 12·90, 12·96, 13·02 (vs triplet), 15·1 (vs).
$EtO \cdot NO_2$ (C.S. 85*) Main bands	3·35, 3·45 (s doublet), 6·12 (vs), 6·90 (m), 7·30 (m), 7·80 (vs), 9·87 (vs), 11·0 (vs), 11·6 (vs), 13·14 (m), 14·23 (m).

where m = medium, s = strong, vs = very strong, w = weak.

* See footnote, Part XIII, p. 916.

University Chemical Laboratory, Cambridge. [*Received, October 27th*, 1953.]

*Addition of Free Radicals to Unsaturated Systems. Part VII.** 1 : 1-*Difluoroethylene.*

By R. N. Haszeldine and B. R. Steele.

[Reprint Order No. 4819.]

The photochemical reaction of trifluoroiodomethane with 1 : 1-difluoroethylene yields only the compound $CF_3{\cdot}CH_2{\cdot}CF_2I$, *i.e.*, the trifluoromethyl radical attacks exclusively the $:CH_2$ group. Proof of constitution is given. Iodine monobromide and 1 : 1-difluoroethylene yield only 1-bromo-1 : 1-difluoro-2-iodoethane; the iodo-compound is converted into 1 : 1 : 1-trifluoro-2-iodoethane by means of mercurous fluoride.

The direction of addition of a trifluoromethyl radical, derived from trifluoroiodomethane, to vinyl chloride and vinyl fluoride was shown to be exclusively to the $:CH_2$ group (Part II, *J.*, 1953, 1199). The present study is concerned with the highly polarised olefin 1 : 1-difluoroethylene.

Trifluoroiodomethane and 1 : 1-difluoroethylene show no dark reaction, but react smoothly on exposure to light of wave-length >3000 Å, with liberation of only traces of iodine, to give exclusively $CF_3{\cdot}(C_2H_2F_2){\cdot}I$. Light of wave-length >2200 Å (silica reaction vessels) appreciably increases the rate of formation of $CF_3{\cdot}(C_2H_2F_2){\cdot}I$; small amounts of products of higher boiling point are also formed. Infra-red spectroscopic examination shows that the two products $CF_3{\cdot}(C_2H_2F_2){\cdot}I$ are identical. The product is formed by a chain reaction of the type postulated earlier :

$$CF_3I \xrightarrow{h\nu} CF_3{\cdot} + I{\cdot}$$

$$CF_3{\cdot} + C_2H_2F_2 \longrightarrow CF_3{\cdot}(C_2H_2F_2){\cdot} \xrightarrow{CF_3I} CF_3{\cdot}(C_2H_2F_2){\cdot}I + CF_3{\cdot}$$

and could be (I) or (II). That it is 1 : 1 : 1 : 3 : 3-pentafluoro-3-iodopropane (I), to an extent of at least 85% and probably exclusively, is shown by its dehydroiodination by

$$\underset{\text{(I)}}{CF_3{\cdot}CH_2{\cdot}CF_2I} \qquad \underset{\text{(II)}}{CF_3{\cdot}CF_2{\cdot}CH_2I} \qquad \underset{\text{(III)}}{CF_3{\cdot}CH{:}CF_2}$$

means of solid potassium hydroxide to give a high yield of the known 1 : 1 : 3 : 3 : 3-pentafluoropropene (III). 1 : 1 : 1 : 2 : 2-Pentafluoro-3-iodopropane (II) would not be converted into (III) by this method. The dehydroiodination can also be effected by means of ethanolic potassium hydroxide, but the yields of the olefin are considerably reduced, since formation of an ether occurs :

$$\text{(I)} \longrightarrow \text{(III)}$$

$$EtO^- + CF_3{\cdot}CH{:}CF_2 \longrightarrow CF_3{\cdot}\bar{C}H{\cdot}CF_2{\cdot}OEt \xrightarrow{EtOH} CF_3{\cdot}CH_2{\cdot}CF_2{\cdot}OEt + EtO^-$$

The susceptibility of fluoro-olefins to nucleophilic attack and the resistance of compounds which contain a CF_2I group to S_N2 reactions are well established. Clear distinction between (I) and (II) can also be made from the ultra-violet spectra in light petroleum shown in the annexed Table.

	$\lambda_{max.}$	ε	$\lambda_{min.}$	ε		$\lambda_{max.}$	ε	$\lambda_{min.}$	ε
$CF_3{\cdot}CF_2{\cdot}CF_2I$	271	240	215	13	$CF_3{\cdot}CH_2I$ ...	262	265	—	—
$CF_3{\cdot}CH_2{\cdot}CF_2I$	271	290	219	24	$CF_2Cl{\cdot}CH_2I$...	263	500	212	20
$CH_2Cl{\cdot}CF_2I$ ...	269	340	228	55	$CF_2Br{\cdot}CH_2I$	266	420	239	230

The ultra-violet absorption maximum of 1-chloro-2 : 2-difluoro-2-iodoethane at 269 mμ is shifted only slightly to the blue relative to a fully-fluorinated iodo-compound (*e.g.*, C_3F_7I). The maximum for (I), at 271 mμ, is thus at the predicted position. By contrast, a compound of the type $R{\cdot}CH_2I$ (where R = perfluoroalkyl) will have an absorption maximum close to that for 1 : 1 : 1-trifluoro-2-iodoethane (262 mμ), and the difference between the spectra

* Part VI. Jander and Haszeldine, *J.*, 1954, 696.

of compounds $\geqslant C{\cdot}CH_2{\cdot}CF_2I$ and $\geqslant C{\cdot}CF_2{\cdot}CH_2I$ is sufficiently large to be used diagnostically (see also *J.*, 1953, 1764).

The direction of addition of ionic reagents to 1 : 1-difluoroethylene was established by reaction with iodine monobromide. The product is 1-bromo-1 : 1-difluoro-2-iodoethane (IV), since when the iodine is replaced by chlorine, only 1-bromo-2-chloro-1 : 1-difluoroethane (V) is obtained. The infra-red spectrum of (V) is identical with that of the product from hydrogen bromide and 1-chloro-2 : 2-difluoroethylene (unpublished results); this reaction could not yield the 1-bromo-2-chloro-2 : 2-difluoroethane (VI) which would have been obtained from 1 : 1-difluoroethylene if the direction of addition of iodine monobromide had been reversed:

$$CF_2{:}CH_2 \xrightarrow{I^+Br^-} \underset{(IV)}{CF_2Br{\cdot}CH_2I} \xrightarrow{Cl_2} \underset{(V)}{CF_2Br{\cdot}CH_2Cl} \xleftarrow{HBr} CF_2{:}CHCl$$

cf.
$$CF_2{:}CH_2 \xrightarrow{IBr} CF_2I{\cdot}CH_2Br \longrightarrow CF_2Cl{\cdot}CH_2Br \quad (VI)$$

Although 1-bromo-1 : 1-difluoro-2-iodoethane (IV) contains a carbon–iodine bond which is (presumably) weaker than the carbon–bromine bond by 11—12 kcal./mole, reaction of (IV) with mercurous fluoride causes exclusively replacement of *bromine* by fluorine, to give the known 1 : 1 : 1-trifluoro-2-iodoethane ($CF_2Br{\cdot}CH_2I \longrightarrow CF_3{\cdot}CH_2I$); 1 : 1-difluoroethylene is a major by-product. This shows that the presence of other halogen, and the absence of hydrogen, on the carbon atom carrying the halogen atom to be replaced, has a marked influence on the ease of reaction.

Discussion.—The main factor influencing the direction of addition of the trifluoromethyl radical to 1 : 1-difluoroethylene is considered to be the relative stabilities of the intermediate radicals $CF_3{\cdot}CH_2{\cdot}CF_2{\cdot}$ and $CF_3{\cdot}CF_2{\cdot}CH_2{\cdot}$, but a full discussion of the factors affecting the stability of these and other radicals is deferred to a later paper.

Two alternative suggestions may be considered at this stage and discarded: A mechanism which could be invoked to explain certain of the results recorded earlier in this series is that the addition occurs *via ionic* intermediates $CF_3^-\ I^+$ from trifluoroiodomethane. Thus, for chlorotrifluoroethylene, $\overset{\delta-}{CF_3}\overset{\delta+}{I} + \overset{\delta+}{CF_2}{:}\overset{\delta-}{CFCl} \longrightarrow CF_3{\cdot}CF_2{\cdot}CFClI$ as actually found (Part III). The mechanism is clearly wrong, however, since, apart from arguments against ionic mechanisms given in earlier papers, the present communication shows that 1 : 1-difluoroethylene yields $CF_3{\cdot}CH_2{\cdot}CF_2I$, whereas by the ionic mechanism $CF_3{\cdot}CF_2{\cdot}CH_2I$ would have been produced.

A second concept which has to be considered is that the trifluoromethyl radical might attack the olefinic carbon atom which which it will form the stronger bond. Thus, since the CF_2–CF_2 carbon–carbon bond in a fluorocarbon is very probably stronger than that in CH_2–CH_2 in a hydrocarbon, it could be argued that the free radical would attack a $:CF_2$ group in preference to a $:CH_2$ group, or to a :CFCl or –CF: group. Although this theory would predict the product successfully for $CF_2{:}CFCl$ ($\longrightarrow CF_3{\cdot}CF_2{\cdot}CFClI$) or $CF_3{\cdot}CF{:}CF_2$ ($\longrightarrow CF_3{\cdot}CFI{\cdot}CF_2{\cdot}CF_3$), it fails with 1 : 1-difluoroethylene, and is therefore considered unsuitable for general application.

Experimental

The reaction vessels were sealed Pyrex or silica tubes which were filled from a vacuum system, and sealed *in vacuo*. Care was taken to exclude air, moisture, etc., which might catalyse ionic or free-radical reactions. The products were distilled in a vacuum-system or in short fractionating columns designed to give minimum hold-up. Trifluoroiodomethane (*J.*, 1951, 584), hydrogen bromide, hydrogen chloride, and chlorine were dried and stored *in vacuo* before use.

Reaction of 1 : 1-*Difluoroethylene with Trifluoroiodomethane.*—The olefin was a commercial specimen which was further purified by distillation *in vacuo* (Found: *M*, 64·0. Calc. for $C_2H_2F_2$: *M*, 64·0); its purity was checked by infra-red spectroscopic examination, and it was peroxide-free.

(a) *In Pyrex vessels.* The olefin (5·1 g., 0·079 mole) and trifluoroiodomethane (14·8 g., 0·076 mole) were exposed to ultra-violet light for 28 days in a Pyrex vessel (capacity 600 ml.)

the lower portion of which was shielded. Fractionation gave unchanged reactants (7·0 g.) and liquid products (12·6 g.) which were redistilled, to give 1 : 1 : 1 : 3 : 3-*pentafluoro-3-iodopropane* (11·6 g., 90%), b. p. 72·0°, n_D^{20} 1·373 (Found: C, 14·1; H, 1·1. $C_3H_2F_5I$ requires C, 13·9; H, 0·8%) (infra-red spectrum, C.S. 98*).

(b) *In silica vessels.* Irradiation for 4 days of trifluoroiodomethane (13·5 g., 0·069 mole) and the olefin (4·2 g., 0·066 mole) in a 200-ml. silica vessel gave unchanged trifluoroiodomethane (1·5 g.) and 1 : 1 : 1 : 3 : 3-pentafluoro-3-iodopropane (13·2 g., 83%), identical with that obtained as in (a) above, and a fraction of higher b. p. (2·0 g.).

Dehydroiodination of 1 : 1 : 1 : 3 : 3-*Pentafluoro-3-iodopropane.*—The iodo-compound (4·0 g.) was slowly added to powdered potassium hydroxide (10 g.) in a Pyrex flask fitted with a water condenser, and after 4 hours' heating to 100° the volatile products were swept out by a stream of dry nitrogen and transferred to a vacuum-system. Distillation gave 1 : 1 : 3 : 3 : 3-pentafluoropropene (1·70 g., 85%), b. p. −20·7° (Found: *M*, 132. Calc. for C_3HF_5: *M*, 132), identified by means of its infra-red spectrum (C.S. 100*). Henne and Waalkes (*J. Amer. Chem. Soc.*, 1946, **68**, 496) report b. p. −21°.

Treatment of 1 : 1 : 1 : 3 : 3-pentafluoro-3-iodopropane (6·0 g.) with 10% ethanolic potassium hydroxide (20 ml.) at room temperature (2 hr.), then at 80° (2 hr.), gave volatile products which were washed with water and distilled, to give 1 : 1 : 3 : 3 : 3-pentafluoropropene (1·02 g., 34%) (Found: *M*, 133. Calc. for C_3HF_5: *M*, 132), identified by means of its infra-red spectrum. The contents of the reaction flask were treated with an excess of water, and the lower layer was dried (P_2O_5) and distilled, to give 1-*ethoxy*-1 : 1 : 3 : 3 : 3-*pentafluoropropane* (1·0 g., 25%), b. p. 77°, n_D^{20} 1·326 (Found: C, 33·6; H, 3·8. $C_5H_7OF_5$ requires C, 33·7; H, 3·9%), shown by its infra-red spectrum to be very slightly contaminated by an olefin. Treatment of the ether with chlorine in an attempt to remove the olefin caused extensive breakdown.

Reaction of 1 : 1-*Difluoroethylene with Iodine Monobromide.*—The olefin (7·5 g., 0·12 mole) and iodine monobromide (24 g., 0·12 mole) were set aside for 24 hr. in the dark. The liquid product (31 g.) was shaken with aqueous sodium thiosulphate and distilled from phosphoric anhydride, to give 1-*bromo*-1 : 1-*difluoro*-2-*iodoethane* (30 g., 95%), b. p. 84°/216 mm., n_D^{20} 1·504 (Found: C, 9·1; H, 0·7. $C_2H_2BrF_2I$ requires C, 8·8; H, 0·7%). C.S. 99*.

The iodo-compound (2·0 g., 0·007 mole) was sealed with chlorine (0·52 g., 0·007 mole), set aside in the dark for 1 day, then exposed to ultra-violet light for 1 day. After treatment with mercury the product was distilled, to give 1-bromo-2-chloro-1 : 1-difluoroethane (1·10 g., 83%), b. p. 71°/770 mm., n_D^{20} 1·404. The infra-red spectrum of this compound (C.S. 101*) was identical with that of the compound prepared by the reaction of hydrogen bromide with 1-chloro-2 : 2-difluoroethylene.

Reaction of 1-*Bromo*-1 : 1-*difluoro*-2-*iodoethane with Mercurous Fluoride.*—The iodo-compound (3·50 g.) was heated at 140° during 4 hr. with mercurous fluoride (20 g.) in a Pyrex flask fitted with an air-condenser connected *via* glass tubing to a trap cooled in liquid oxygen. Dry nitrogen was then passed into the flask, and the condenser and connecting tube were heated so that material of b. p. <100° distilled into the trap. Distillation of the product *in vacuo* give 1 : 1 : 1 trifluoro-2-iodoethane (1·44 g., 53%), b. p. 55·0° (Found: *M*, 209. Calc. for $C_2H_2F_3I$: *M*, 210), 1 : 1-difluoroethylene (0·275 g., 33%), and a small amount of silicon tetrafluoride. Gilman and Jones (*J. Amer. Chem. Soc.*, 1943, **65**, 2037) report b. p. 54·5—55·0°/730 mm. for 1 : 1 : 1-trifluoro-2-iodoethane.

The authors thank Allied Chemical and Dye Corporation General Chemical Division for a gift of 1 : 1-difluoroethylene. One of them (B. R. S.) is indebted to the Department of Scientific and Industrial Research for a Maintenance Allowance.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, November 20th*, 1953.]

* Spectra thus marked have been deposited with the Society. Photocopies, price 3*s.* 0*d.* per copy per spectrum, post free, may be obtained on application to the General Secrerary, stating the C.S. number.

The Thermal Oxidation of Hydrazine Vapour.

By W. I. H. WINNING.

[Reprint Order No. 3405.]

The thermal gas-phase reaction between hydrazine and oxygen shows none of the chain characteristics of, *e.g.*, the hydrocarbon series. It is a predominantly surface reaction, the activation energy of which, below 100°, was found to be 6430 cal./mole.

On comparison with the absolute reaction-rate expression for a bimolecular surface reaction, unretarded by the products, and in which neither reactant is strongly adsorbed, very good agreement is obtained between the experimental and the theoretical rate value.

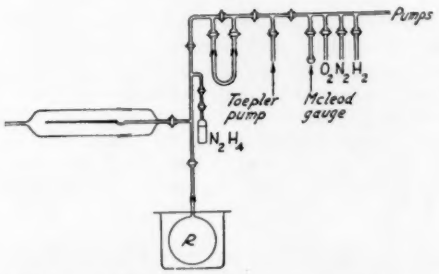
HYDRAZINE has recently received considerable prominence as a propellent, when combined with a suitable oxidiser (Audrieth and Ogg, " The Chemistry of Hydrazine," Wiley, New York, 1951). Surprisingly few data are available on its oxidation, and these are mainly concerned with the liquid-phase reaction. Two investigations have been made on the order of the vapour-phase reaction: in one, the rate was found to be of first order with respect to both hydrazine and oxygen, and proportional to the half-power of the water concentration (Nelson and Holcomb, U.S. Project Tech. Memo. No. PUR-7). In the other, Bowen and Birley (*Trans. Faraday Soc.*, 1951, **47**, 580) confirmed the initial first-order rate and suggested a mechanism for the reaction.

The present examination has been made primarily to measure the fundamental properties of the reaction, its velocity constants and activation energy, and to find whether it takes place in the gas phase or heterogeneously, and whether it possesses a chain mechanism or not. A value of the reaction order more in agreement with that of the second investigation has been assigned for the present conditions.

EXPERIMENTAL

A static system was set up, as shown diagrammatically in Fig. 1, in which the main reaction vessel, *R*, was a 2-l. quartz flask. To determine the effect of surface : volume ratio, two vessels

FIG. 1.



were used, a similar one of Pyrex glass, and its ½-l. counterpart. These led directly to a manometer, with a glass-membrane gauge to prevent contamination of the reactants by mercury vapour. The hydrazine was stored nearby, after first being purified by distillation, and then transferred to a tube in the same manner. On the main gas line were attached a McLeod gauge and leads to the Toepler pump and gas-analysis section and to the gas storage bulbs.

Since hydrazine reacts slowly with oxygen even at room temperature, a sufficient variation in temperature was produced by an oil-bath, surrounding the reaction vessel and heated electrically.

In a typical run, the hydrazine was introduced from the side-tube, and its vapour pressure measured by the glass-membrane gauge. Oxygen was added immediately afterwards, at a pressure equal to, or in slight excess of, that required by the equation $N_2H_4 + O_2 = N_2 + 2H_2O$. In the experiments with water vapour, this was introduced immediately after the hydrazine. Nitrogen, when added as an inert gas, was the final substance to enter the vessel.

Reaction periods lay in the range from 3 to 300 min. The less volatile products were frozen out by a trap at −180°, situated between the reaction vessel and the Toepler pump. The nitrogen formed, which was the only product not to be removed in this way, could be collected and its volume measured, after combustion of the residual oxygen. The condensed products were dissolved in distilled water and titrated for total base and hydrazine itself with potassium iodate (Penneman and Audrieth, *Analyt. Chem.*, 1948, **20**, 1058). In this way, the presence of ammonia was unmistakably shown in the experiments conducted at the higher temperatures (Figs. 2 and 3).

Results.—(1) Early experiments with a small (100-ml.) vessel showed that adsorption effects were present, and that the surface played a considerable part in the reaction. In a 2-l. flask, results became more reproducible. Conditions eventually became steady, and it was in those circumstances that the data for determination of k and "E (apparent)" were obtained. The

TABLE 1. *2-Litre vessel (quartz.)*

Temp.	Time * (min.)	$[N_2H_4]$ (unchanged) (10^4 mole/l.)	$-d[N_2H_4]/dt$ (10^4 mole $l.^{-1}$ $sec.^{-1}$)	k (l. $mole^{-1}$ $sec.^{-1}$)
185°	0	3·89	—	—
	5	2·57	—	—
	10	1·98	—	—
	10 (g)	1·87	2·17	6·21
	20	1·16	—	—
	20 (g)	1·13	0·78	6·11
	40	0·59	—	—
	40 (g)	0·57	0·20	6·15
185 (vessel KCl-coated)	0	4·37	—	—
	5	2·97	—	—
	12	2·10	—	—
	15	1·14	—	—
	25	0·65	—	—
115	0	4·80	—	—
	20	3·95	—	—
	25 (g)	3·55	0·83	0·659
	35	3·17	—	—
	50	3·20	—	—
	50 (g)	2·70	0·43	0·590
	100 (g)	1·80	0·20	0·616
	135	1·56	—	—
55	0	4·25	—	—
	40	3·22	—	—
	50 (g)	3·28	0·20	0·186
	90	3·03	—	—
	100 (g)	2·79	0·12	0·154
	150 (g)	2·50	0·083	0·133
	240	2·14	—	—
20	5	3·70	—	—
	5	3·39	—	—
	45	3·56	—	—
	80	3·12	—	—
	100 (g)	3·16	0·067	0·067
	120	3·20	—	—
	180	2·94	—	—
	250 (g)	2·65	0·057	0·069
	285	2·56	—	—

* (g) = Value from graph.

rates of disappearance of hydrazine were determined from the graphs, by tangents to the lines after various time intervals.

The extent of ammonia formation (expressed in the usual concentration units) at 115° and 185° is plotted in Figs. 2 and 3. That the effect was not due to decomposition of the hydrazine at the temperatures concerned was shown from the corresponding reaction in the absence of oxygen, and also with excess of nitrogen present, the hydrazine being quantitatively recovered.

When $\ln k$ was plotted against $1/T$ (Fig. 4), the apparent energy of activation of 8360 cal./mole was found for the temperature range 20—185° : between 20° and 115°, it is 6430 cal./mole.

(2) *Heterogeneity of the reaction.* Although certain previous results (Nelson and Holcomb, *loc. cit.*) were interpreted on the assumption of a homogeneous reaction, the effect of packing the vessel with glass-wool showed this not to be the case. It was found, however, that coating

FIG. 2.

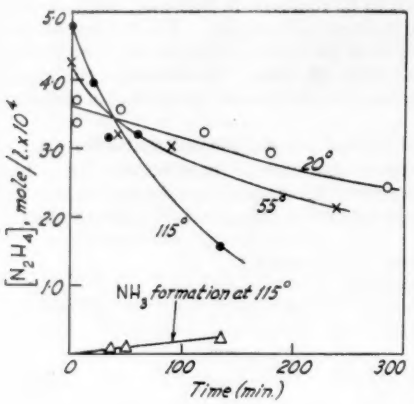
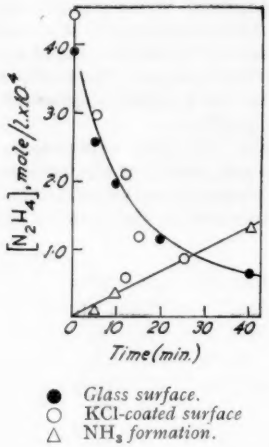


FIG. 3. *At* 185°.



● *Glass surface.*
○ KCl-*coated surface*
△ NH_3 *formation.*

FIG. 4.

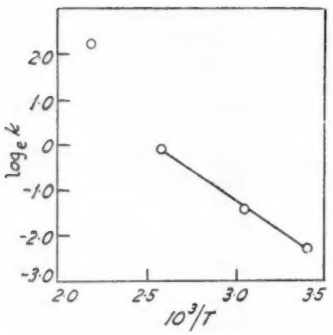
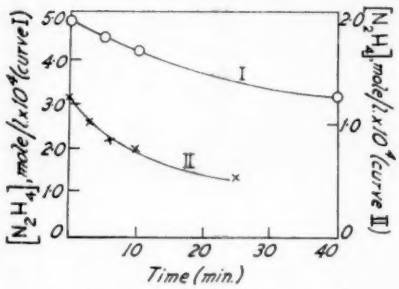


FIG. 5.



I, 2-*litre vessel.* II, ½-*litre vessel.*

FIG. 6.

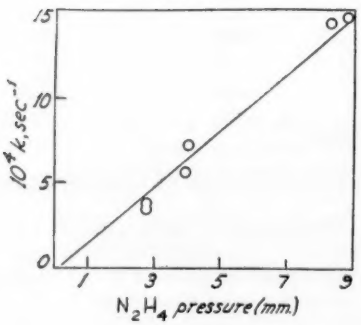
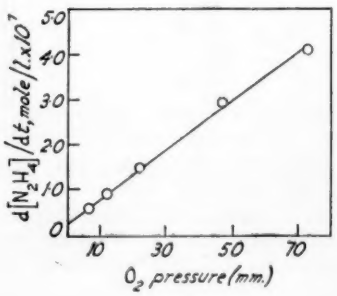


FIG. 7.



the surface with potassium chloride by the normal procedure, although exerting a strong retardation of the corresponding reaction with ammonia (Stephens and Pease, *J. Amer. Chem. Soc.*, 1950, **72**, 1188), left the rate unaffected in the present instance.

The effect of surface was investigated quantitatively by use of two Pyrex vessels, alike in all respects except volume. They were first carefully cleaned with concentrated nitric acid and

TABLE 2. *Temperature* = 25°.

Time (min.)	$[N_2H_4]$ (unchanged) (10^4 mole/l.)	$-d[N_2H_4]/dt$ (10^7 mole l.$^{-1}$ sec.$^{-1}$)	k (l. mole^{-1} sec.$^{-1}$)	Time (min.)	$[N_2H_4]$ (unchanged) (10^4 mole/l.)	$-d[N_2H_4]/dt$ (10^7 mole l.$^{-1}$ sec.$^{-1}$)	k (l. mole^{-1} sec.$^{-1}$)
½-Litre vessel (Pyrex).				2-Litre vessel (Pyrex).			
0	1·26	—	—	0	4·90	—	—
3	1·03	—	—	5	4·53	—	—
5 (g)	0·93	0·71	0·770	10	4·15	—	—
6	0·89	—	—	10 (g)	4·16	0·86	0·474
10	0·80	—	—	20 (g)	3·69	0·65	0·477
10 (g)	0·75	0·42	0·740	30 (g)	3·34	0·50	0·448
15 (g)	0·63	0·29	0·731	40	3·13	—	—
25	0·54	—	—			Average value =	0·466
		Average value =	0·747				

$$\frac{k\ (\frac{1}{2}\text{-l.})}{k\ (2\text{-l.})} = \frac{0{\cdot}747}{0{\cdot}466} = 1{\cdot}60. \qquad \frac{\text{Surface/volume } (\frac{1}{2}\text{-l.})}{\text{Surface/volume } (2\text{-l.})} = 1{\cdot}59.$$

distilled water, by an identical procedure. The rate agreed almost exactly with the theoretical value, direct proportionality to the surface area being assumed (Fig. 5 and Table 2). Hydrazine and oxygen pressures were again equated, within experimental limits.

(3) *Variation of hydrazine pressure.* With 2·7—8·8 mm. of hydrazine and excess (50 mm.) of oxygen, the times of half-conversion of the hydrazine were measured, and the first-order velocity constants derived. Direct proportionality between the rate and hydrazine concentration was found (Fig. 6 and Table 3).

TABLE 3. *Temperature* = 25°. 2-*Litre vessel* (*quartz*).

Initial oxygen concn. = 2·94 × 10^{-3} mole/l.

$[N_2H_4]$ (unchanged) (10^4 mole/l.)	Time (min.)	k (10^4 sec.$^{-1}$)	$[N_2H_4]$ (unchanged) (10^4 mole/l.)	Time (min.)	k (10^4 sec.$^{-1}$)
1·55	0	—	2·30	0	—
0·99	20	3·74	1·18	15	7·26
0·71	30	3·77			
			4·77	0	—
2·25	0	—	2·63	7	14·2
1·35	15	5·56			
			5·08	0	—
			2·13	10	14·5

(4) *Variation of oxygen pressure.* At a fixed hydrazine pressure (7·5 mm.), oxygen pressure was varied from 6·5 to 72·5 mm. The time of reaction was taken, so that the ΔN_2H_4 value lay consistently within a narrow range. The rate of reaction was in almost direct proportion to the oxygen concentration (Fig. 7 and Table 4).

TABLE 4. *Temperature* = 25°. 2-*Litre vessel* (*quartz*).

Initial hydrazine concn. = 4·42 × 10^{-4} mole/l.

$[O_2]$, mm.	Time (min.)	ΔN_2H_4 (10^4 mole/l.)	$-d[N_2H_4]/dt$ (10^7 mole l.$^{-1}$ sec.$^{-1}$)	$[O_2]$, mm.	Time (min.)	ΔN_2H_4 (10^4 mole/l.)	$-d[N_2H_4]/dt$ (10^7 mole l.$^{-1}$ sec.$^{-1}$)
6·5	70	2·60	(0·62)	47·5	15	2·59	2·88
12	50	2·79	0·93	72·5	10	2·46	4·10
22	30	2·64	1·47				

(5) *Effect of added nitrogen and water vapour.* No accelerating or retarding action was observed on the addition of excess of either substance (see Table 5).

TABLE 5. *Temperature* = 25°. *2-Litre vessel (quartz).*

[Inert] gas], mm.	Time (min.)	ΔN_2H_4 (10^4 mole/l.)	$\frac{\Delta N_2H_4 \text{ (normal)}}{\Delta N_2H_4 \text{ (added gas)}}$	[Inert gas], mm.	Time (min.)	ΔN_2H_4 (10^4 mole/l.)	$\frac{\Delta N_2H_4 \text{ (normal)}}{\Delta N_2H_4 \text{ (added gas)}}$
Nitrogen.				Water vapour.			
Initial N_2H_4 concn. = $5{\cdot}77 \times 10^{-4}$ mole/l.				Initial N_2H_4 concn. = $2{\cdot}42 \times 10^{-4}$ mole/l.			
—	60	2·59	—	—	60	1·07	—
200	60	2·48	1·04	10	60	1·09	0·98
—	120	4·33	—	—	60	1·24	—
200	120	4·63	0·94	8	60	1·14	1·09

DISCUSSION

None of the criteria of a chain mechanism was observed at any stage in this investigation. Reaction appeared to commence immediately on mixing of the reactants, with no induction period. Addition of excess of the product gases did not affect the rate.

The rate increased linearly with the oxygen concentration, and this, taken in conjunction with other results, strongly suggests a non-chain bimolecular process.

When considered on this basis, in terms of the absolute reaction rate theory, the agreement between the theoretical and the experimental values was very good, particularly in comparison with other classical examples.

In confirmation of previous investigations (Bowen and Birley; Nelson and Holcomb; *locc. cit.*), the rate was shown to be of first order with respect to both oxygen and hydrazine, and independent of the nitrogen concentration. However, when an excess of water vapour was added, no increase in rate was observed, possibly owing to the very different experimental conditions.

That dimerisation of the hydrazine vapour might take place (Giguère and Rundle, *J. Amer. Chem. Soc.*, 1941, **63**, 1135) was considered, but the correspondence between the pressure of hydrazine as recorded on the manometer and the amount recovered by the method previously described excluded this at the temperatures and pressures concerned.

From the plot of ln k against 1/T (Fig. 4), a slightly greater activation energy is indicated at the higher temperature range (8·5 kcal./mole, to be compared with 6·5 below 100°). This can be accounted for if it is assumed that the gas-phase reaction is coming into effect: alternatively, it may be connected with the formation of small amounts of ammonia under these conditions. On the basis of a heat of activation of 38 kcal./mole, Bowen and Birley (*loc. cit.*) postulate the presence of short reaction chains as the operative mechanism.

The main results in the present work show a bimolecular surface reaction, unretarded by the products. They have been compared with the values obtained from the appropriate absolute reaction rate expression, in which the reactants are adsorbed to a comparable extent (Glasstone, Laidler, and Eyring, " Theory of Rate Processes," McGraw-Hill, New York, 1941), *viz.*,

$$v = \tfrac{1}{2} s C_{N_2H_4} C_{O_2} C_S \frac{kT}{h} \frac{f^*}{f_S} \frac{1}{F_{N_2H_4} F_{O_2}} e^{-\varepsilon_0/kT}$$

When the terms for the partition functions of a non-linear polyatomic molecule and of oxygen are included, this becomes

$$v = \tfrac{1}{12} C_{N_2H_4} C_{O_2} C_S \frac{f_S}{f^*} \frac{\sigma_{N_2H_4}\sigma_{O_2}}{(\sigma^*)^2(8\pi^2)^2} \frac{s^3 h^{10}}{(8\pi^3 ABC)^{\frac{1}{2}} I (2\pi m)^3 (kT)^{\frac{11}{2}}} e^{-\varepsilon_0/kT}$$

the symbols possessing their usual significance (*op. cit.*).

With the generally accepted approximations in regard to the partition functions and symmetry numbers of the reactants and activated complex, and substitution of the values of the constants and other data, this becomes

$$v = \frac{2{\cdot}31 \times 10^{-3}}{T^{\frac{11}{2}}} [N_2H_4][O_2] e^{-E_0/RT} \text{ mole cm.}^{-2} \text{ sec.}^{-1}$$

The corresponding rates from Table 1 are tabulated in Table 6 for the temperature 55°, under the heading $v_{theor.}$, along with the experimental rates, expressed in the same units

for a reaction vessel of 2-l. capacity and 768 sq. cm. surface area. The value for the energy of activation (6430 cal./mole) from the results at the lower temperature range was preferred

TABLE 6. *Temperature* = 55°. *2-Litre vessel (quartz).*

Initial N_2H_4 concn. = $5{\cdot}02 \times 10^{-4}$ mole/l.

Time, min.	50	100	150
$10^{13}v_{expt.}$, molecules cm.$^{-3}$ sec.$^{-1}$	5·2	3·1	2·2
$10^{13}v_{theor.}$,,	4·5	3·3	2·6

to the overall figure, for the reason previously adduced. No further modification was made for temperature.

The author thanks the U.S. Navy Bureau of Ordnance and Office of Naval Research for a Research Associateship, during the tenure of which the above investigation was carried out; and Professors H. S. Taylor and R. N. Pease for their interest throughout.

FRICK CHEMICAL LABORATORY, PRINCETON, NEW JERSEY.
[Present address: MACLEANS LTD., BRENTFORD, MIDDLESEX. [*Received, May 21st,* 1952.]

Paracyanogen: Its Formation and Properties. Part I.

By L. L. BIRCUMSHAW, F. M. TAYLER, and D. H. WHIFFEN.

[Reprint Order No. 4649.]

The brown residue, obtained by heating oxamide for several hours in a sealed tube, has been shown to be paracyanogen. The chemical and physical properties and infra-red spectra have been compared with those of paracyanogen prepared by thermal decomposition of mercuric and silver cyanides. Some suggestions are put forward with regard to its structure.

IN an attempt to grow large crystals of oxamide by slow sublimation a brown residue was found in the hot section of the sublimation tube. It was suspected that this was paracyanogen. The substance was therefore compared with paracyanogen from other sources. These compounds are little known and their structures are undetermined.

Paracyanogen was first noticed by Guy Lussac (*Annalen*, 1816, **53**, 139) during his experiments on heating mercuric cyanide, which led to the discovery of cyanogen. He considered the material to be mainly carbon with a small nitrogen content. Johnston (Brewster's *Edinburgh J. Sci.*, New Series, 1829, **1**; *Trans. Roy. Soc. Edinburgh*, 1840, **14**, 30) reported most of the known properties of paracyanogen. Paracyanogen is most easily prepared from mercury cyanide, and Troost and Hautefeuille (*Compt. rend.*, 1868, **66**, 738) found the optimum conditions were to heat the salt for two days at 440°. It may also be prepared by heating silver cyanide (Redtenbacher and Liebig, *Annalen*, 1844, **50**, 357), silver cyanate (Johnston, *loc. cit.*), cyanogen iodide (Klason, *Ber.*, 1866, **18**, 496), or cyanuric iodide (Bowden and Williams, *Proc. Roy. Soc.*, 1951, *A*, **208**, 176). Paracyanogen has been made by thermal polymerisation of cyanogen under various conditions by Briner and Wroczynski (*Compt. rend.*, 1910, **151**, 314), Perret and Krawczynski (*Bull. Soc. chim.*, 1932, **51**, 622), Jerwen (*Z. physikal. Chem.*, 1916, **91**, 494), and Berthelot and Gaudechon (*Compt. rend.*, 1910, **150**, 1171). Photopolymerisation of cyanogen has been reported (Hogness and Lin-sheng Ts'ai, *J. Amer. Chem. Soc.*, 1932, **54**, 123), as has polymerisation initiated by α-particles (Lind and Bardwell, *Science*, 1925, **62**, 593). Paracyanogen can be produced by electrolysis of potassium cyanide solutions (Hittorf, *Z. physikal. Chem.*, 1892, **10**, 616), by passing hydrogen cyanide or cyanogen into water and igniting the brown precipitate produced (Johnston, *loc cit.*), and by ignition of the precipitate formed when saturated solutions of cyanogen in concentrated aqueous potassium hydroxide or in ether or ethanol (Johnston, *loc. cit.*) are kept. All the investigators found great difficulties in the analysis of their products.

Experimental

Paracyanogen has been found to be formed by a solid-phase polycondensation reaction when oxamide is heated in a sealed glass tube at 250—300°. Oxamide (0·5 g.) in a small sample tube (open at one end) was placed inside a hard-glass tube, 1·2 cm. wide and 10 cm. long, which was then evacuated and sealed with a blow-pipe. Four of these tubes were placed in a steel autoclave together with solid carbon dioxide, 20 g. producing a pressure of about 100 atm. The autoclave was heated in a tubular oven for one week at 270°. After cooling, the glass tubes were opened. The inner sample tubes were heated to 250° for 3 hr. *in vacuo* to remove the residual oxamide by sublimation and also any absorbed water and cyanogen. The conversion was 30—40%. This procedure was adopted for several reasons. The pressure which accumulated in the sealed tube, owing to the vapour pressure of the oxamide and the gaseous products of the reaction, shattered most of the tubes before the compensating autoclave was used. The use of the inner sample tube made the transference of the material from the sealed tube to the high-vacuum apparatus much simpler. Sublimation of the residual oxamide proved an easier method of purification than did washing with hot water. In the final form of the autoclave used, the head, a substantial steel block, was clamped to the body by six high-tensile steel bolts. The contact with the recessed lead washer was made by accurately machined surfaces. The autoclave would withstand a pressure of 130 atm. A Simmerstat of type (TYB) controlled the energy input of the furnace, the temperature remaining within $\pm 1{\cdot}0°$. 25% of the tubes burst; the pressure within the tubes rose continuously so that a satisfactory compensating pressure for a week's heating would be so large that there would be a risk of bursting the tubes in the early stages by too high an excess of pressure. In later experiments only 2 days' heating was given and a 10% yield obtained. The product was dark brown and usually light and porous. Complete polymerisation gave an almost black dense product.

If the inner sample tube was plugged with glass wool, all the product was found inside the inner tube mixed with the oxamide, with only the slightest traces on the walls of the tubes. This shows that the reaction occurs either on the surface of the oxamide or more probably within the crystal by a simple solid-phase condensation. A striking confirmation is given by an electron-microscope photograph (Fig. 1) where the paracyanogen mass is seen growing out of the oxamide crystals.

Preparation of Paracyanogen from Other Sources.—Samples were prepared from mercuric cyanide and from silver cyanide. Either cyanide (5 g.) was placed in a Pyrex tube (1·2 cm. bore, 10 cm. long), which was then evacuated, sealed, and heated for 24 hr. at 440°. After cooling, the tubes were opened by localised heating with a blow-pipe. The silver residues were treated with nitric acid to remove the silver. Then either residue was heated at 300° for 3 hr. *in vacuo* to remove all volatile impurities. Yields were about 80% from mercuric cyanide and 40% from the silver salt. The suffixes (Ox), (Hg), and (Ag) indicate the source of the paracyanogen, *viz.*, oxamide, mercuric cyanide, or silver cyanide.

Analysis of Paracyanogen.—The quantitative analysis of the material proved somewhat difficult owing to its very resistant nature. The normal microchemical methods for the analysis of the carbon and nitrogen proved unsatisfactory. Values of C, 32—34 and N, 32—44% were obtained. Many other methods were tried.

The method finally used was as follows. Paracyanogen (*ca.* 5 mg.) was weighed out on a micro-balance into a Pyrex glass tube of 12 mm. diam. sealed at one end. Potassium sulphate (2 g.), copper sulphate (0·2 g.), and concentrated sulphuric acid were added in such a way that all solid material was washed to the base of the tube. The tube was drawn off, sealed, and heated for 16 hr. at 400°. After cooling, the tubes were opened by cracking, and the acid solution transferred to a standard semi-micro Kjeldahl distillation apparatus, 40% sodium hydroxide being added. The solution was steam-distilled into a saturated boric acid solution (20 c.c.), and and ammonia titrated against N/50-hydrochloric acid with a bromocresol-green–methyl-red indicator. Mean results of four estimations, expressed as percentage of the theoretical nitrogen, were: Paracyanogen (Hg) 96·9%, (Ox) 100·2%.

Chemical Properties.—Paracyanogen is highly resistant to chemical attack. Most of the properties observed by Johnston (*loc. cit.*) have been confirmed. The compound is insoluble in water and most organic liquids. Ignition gives cyanogen or, at much higher temperatures, carbon and nitrogen.

Fusion with potassium gives potassium cyanide, but there is no reaction with fused sulphur or phosphorus. Strong heating in air gives carbon dioxide; in chlorine, cyanogen chloride.

Paracyanogen is soluble in fused potassium hydroxide or in soda-lime to give a deep brown

FIG. 1.

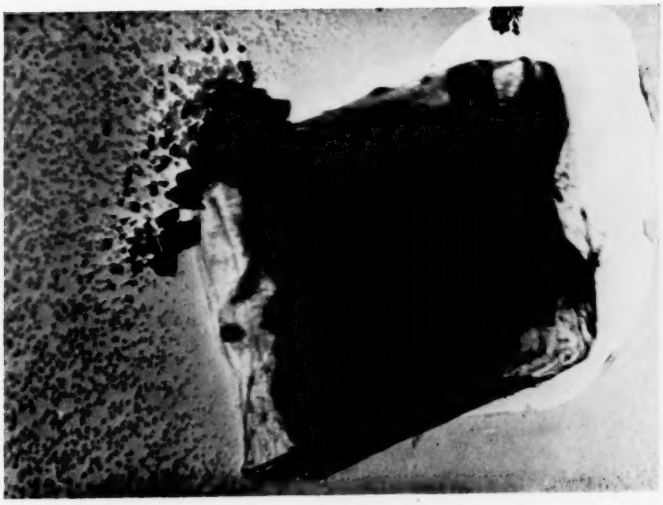
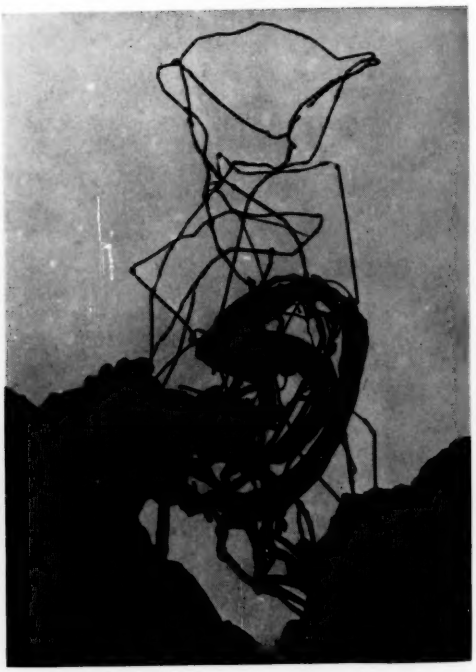


FIG. 3.

[*To face p.* 932.

FIG. 4.

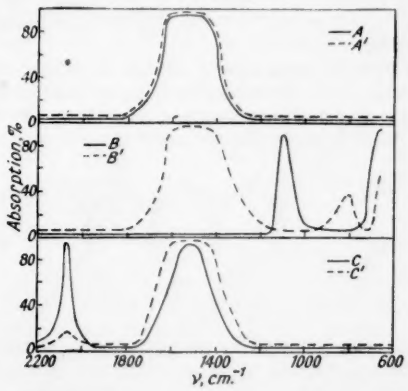


solution which gradually becomes orange-red, then colourless, the solution containing cyanide, cyanate, and carbonate, and ammonia being liberated. It is very slightly soluble in hydrochloric acid but more soluble in concentrated sulphuric acid, from which it is precipitated by water apparently unchanged. The substance is soluble in syrupy phosphoric acid, 60% perchloric acid, and concentrated nitric acid: all these solutions, unlike the solid, exhibit a sky-blue fluorescence in ultra-violet light. The solubility in sulphuric acid is slight, probably less than 1%, although the solution is highly coloured. To make a rough determination of the relative solubilities, a saturated solution in each solvent (2 c.c.) was diluted with water (2 c.c.), and after 24 hr. the relative amounts of precipitate were noted, the sulphuric acid solution being used as a standard. The results for paracyanogen (Ox) were as follows:

Acid used	Colour of solution	Relative wt. of ppt.	Fluorescence
H_2SO_4	Red-brown	10	Sky-blue
H_3PO_4	,,	10	,,
$HClO_4$	,,	8	,,
HNO_3	,,	1	,,
HCl	Faint	Very small	Very faint

Paracyanogen (Ox) dissolved most rapidly in 60% perchloric acid. A much darker solution is given by paracyanogen (Hg) but this is much less easily soluble than paracyanogen (Ox). These sulphuric acid solutions become colourless when heated, cyanogen being evolved.

FIG. 2.



No.	Source and treatment	Absorption frequencies, cm.$^{-1}$	Spectra
1	Paracyanogen (oxamide)	1570 v.s.	*A*
2	,, (mercuric cyanide)	1570 v.s.	*A'*
3	(1) heated to 450° for 24 hr. *in vacuo*	1570 v.s.	as *A*
4	(1) heated to 450° for 16 hr. in air	1100 m., 640 v.s.	*B*
5	(2) heated to 450° for 16 hr. in air	1570 v.s., 810 w., 640 w.	*B'*
6	(1) diss. in conc. H_2SO_4, pptd. by H_2O	2070 v.v.s., 1570 v.s.	*C*
7	(2) diss. in conc. H_2SO_4, pptd. by H_2O	2070 v.w., 1570 v.s.	*C'*
8	(6) heated at 250° for 6 hr. *in vacuo*	2070 w., 1570 v.s.	*C'*
9	(6) heated at 450° for 16 hr. in air	1100 m., 640 v.s.	as *B*
10	(7) heated at 450° for 16 hr. in air	1570 v.s., 810 w., 640 w.	as *B'*
11	Paracyanogen (silver cyanide)	1570 v.s.	as *A'*

Paracyanogen dissolved in fused potassium hydrogen sulphate to give the characteristic deep red-brown solution.

Oxidation Reactions.—If paracyanogen is heated in air at 450° for 16 hr., a brick-red compound of unknown constitution is formed. The normal micro-analysis techniques give variable results for this material. The compounds produced from paracyanogen (Ox) and (Hg) appear to be the same, but their infra-red absorption spectra (Fig. 2) show that they are different. These substances are not produced by similar treatment *in vacuo*, and the amount formed is about 10% by weight of the material used.

The red compound from paracyanogen (Ox), when heated for 1 hr. in a stream of hydrogen, yields a black compound, which on treatment with concentrated sulphuric acid gives a white

insoluble substance. The constitution of neither of these compounds is known and neither fluoresces.

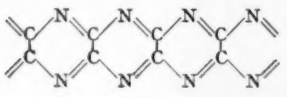
The results obtained by Johnston in the oxidation of paracyanogen by concentrated nitric acid were confirmed. A solution of paracyanogen in concentrated sulphuric acid was added dropwise to boiling nitric acid, giving a pale straw-coloured solution. Addition of mercurous sulphate solution produced a brown flocculent precipitate which gradually formed amber needle-shaped crystals of " mercury paracyanate." Both the acid solution and the mercury derivative gave a sky-blue fluorescence.

Physical Properties of Paracyanogen.—The paracyanogens and some of their derivatives have been examined by infra-red spectroscopy, and by electron microscopy in an attempt to elucidate their structures.

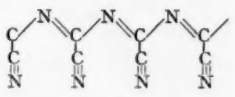
Infra-red absorption spectra. The measurements were made in a Grubb–Parsons spectrometer fitted with a sodium chloride prism. The samples were dispersed in Nujol oil and sandwiched between rock-salt plates. The oil had the twin effects of binding the material and reducing light scatter. The results are shown in the Table and Fig. 2. Some of the bands, especially those at 1570 cm^{-1}, are rather broad and the centres are not very distinct. The intensities given (s. strong, m. medium, w. weak, v.w. very weak) are approximate since it was difficult to keep the absorbing film exactly the same in each case. The numbers in the text refer to the samples in the Table.

The principal paracyanogens, **1**, **2**, **11**, show only the one strong band at 1570 $cm.^{-1}$, which indicates that they have a complete conjugated double-bond system. The spectrum is that which would be expected of a structure such as (I), or particularly the structure with all the C–N bonds equivalent obtained by resonance between this form and that got by interchanging the C–N double and single bonds.

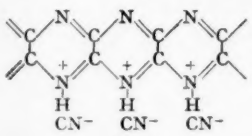
Heating paracyanogen (Ox) *in vacuo* at 450° (**3**) has no effect. Heating in air at the same temperature (**4**) has a profound effect, the residue showing no band at 1570 $cm.^{-1}$ but absorption at 1100 and 640 $cm.^{-1}$ instead. Heating paracyanogen (Hg) (**5**) at 450° in air introduces two weak bands at 810 and 640 $cm.^{-1}$: it is impossible to assign these to any known structural grouping.



(I)



(II)



(III)

Dissolution in sulphuric acid, followed by precipitation in water, also affects the spectra, a new band appearing at 2070 $cm.^{-1}$ which is extremely strong with paracyanogen (Ox) and weak in paracyanogen (Hg). This frequency is too low for absorption by a simple cyanide group (2250 $cm.^{-1}$) or even an *iso*cyanide group (2160 $cm.^{-1}$), though such groups attached to a conjugated system might absorb at lower frequencies. The structure (II) is possible, though a shift of 180 $cm.^{-1}$ on account of conjugation is rather large. Two other cyanide groupings might be considered, adsorbed hydrogen cyanide (gas-state frequency, 2090 $cm.^{-1}$) and cyanide ions (2080 $cm.^{-1}$). The samples were dried in high vacuum so if hydrogen cyanide is present it is tenaciously retained, but salt formation is a possibility (III). The intensity of the 2070 $cm.^{-1}$ band is reduced greatly after 6 hours' heating to 260° *in vacuo* but the band is still detectable in the product.

Heating of the precipitated samples (**6**) and (**7**) in air gave rise to products with the same spectrum as the similar products from their parent paracyanogens, *i.e.*, (**9**) resembles (**4**) and (**10**) resembles (**5**).

To summarise, the paracyanogens are similar in structure though they vary in their resistance to attack. Paracyanogen contains a large conjugated double-bond system and no free cyanide groups, but these might be introduced by treatment with sulphuric acid, possibly owing to some salt formation. Oxidation by air destroys the whole structure.

Electron-microscope Photographs.—The various preparations of paracyanogen were examined under an electron miscroscope. At 9000× magnifications paracyanogen (Ox) appeared as a very crumpled torn film, perhaps owing to a preference for growing in the same plane rather than building up in layers. Fig. 1 shows partly converted oxamide at a magnification of 3500. The zone of decompositions can be clearly seen spreading from the corner of the paracyanogen mass into the oxamide crystals. The growth of a large mass of paracyanogen from the minute

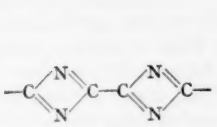
oxamide crystals is remarkable and must mean that the reaction spreads from one crystal to another.

Paracyanogen (Hg) at 12,000× magnification (Fig. 3) has the appearance of frozen droplets. Watson (*J. Phys. Chem.*, **1947**, **51**, 654) noticed that a polymer of hydrogen cyanide, prepared by α-ray bombardment of the gas, when observed under an electron microscope appeared to be an agglomerate of globules. However, paracyanogen (Ag) appeared to be an opaque mass composed of small ill-defined pieces. When an intense beam of electrons was applied to one corner of a large mass a considerable number of fibres unfolded from the mass (Fig. 4, 6500×). The thick inner fibres appeared first. These fibres are similar to those of paracyanogen (Hg).

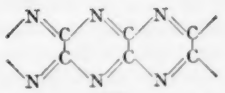
The paracyanogen samples from all three sources, after precipitation from sulphuric acid solution, appeared as shapeless ill-defined masses.

Discussion

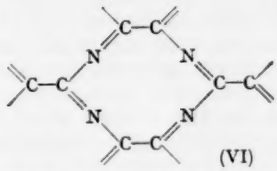
In a solid-phase reaction, such as the formation of paracyanogen from oxamide, those changes which involve least lattice disturbance would be expected to occur most easily. Oxamide has a planar lattice structure (Misch and Van der Wyk, *Compt. rend. Soc. Phys. Hist. Nat. Genève*, **1938**, **55**, 97) with very weak inter-planar bonding but very strong intermolecular bonding within the phase. It is possible then that paracyanogen similarly has a planar structure and all the available evidence supports this theory. On this basis three molecular structures can be drawn, *viz.*, (IV)—(VI). These structures are consistent with the results obtained by infra-red spectroscopy, which indicate the presence of a conjugated double-bond system. A 20-membered ring system can also be drawn but will not be considered further.



(IV)



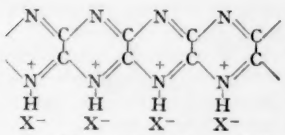
(V)



(VI)

The four-membered ring system (IV) is essentially a linear polymer with free rotation about the C–C bonds. The six-membered ring structure (V) is a " ribbon " polymer, and the ten-membered ring system (VI) an infinite sheet. However, if molecular models are constructed only formula (V) can be made without excessive strain.

In the lattice planes of oxamide the molecules lie in rows linked by hydrogen bonding to form an infinite sheet. From the grouping of molecules in the plane of both the four- and the six-membered ring, structures for paracyanogen could easily be formed by the simple elimination of water across the hydrogen bonds, between adjacent amide groups.



($X^- = HSO_4^-$) (VII)

The fluorescence of the paracyanogen solutions in concentrated mineral acids suggests that a resonating ring structure exists, and that in solution the molecule is ionised, possibly in the form (VII). The solvated multivalent ion is consistent with the intense colouring and the fluorescence of the solutions, and also with the precipitation of paracyanogen on addition of water to the anhydrous acid solutions. Structure (VI) would make paracyanogen unlikely to dissolve; the infinite planar lattice could only accept anions in layers between the planes, forming a colloidal suspension rather than a solution.

We thank Professor J. Sayers and Mr. C. C. Newton for the electron-microscope photographs.

Department of Chemistry, The University,
Edgbaston, Birmingham 15.

[*Received, September 11th*, 1953.]

Synthesis of 9 : 18-*Diaza*isoviolanthrone.

By J. KING and G. R. RAMAGE.

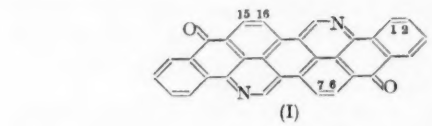
[Reprint Order No. 4767.]

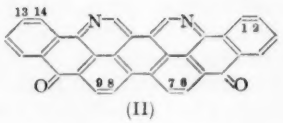
9 : 18-Diaza*iso*violanthrone (I) has been synthesised and its structure confirmed by an alternative synthesis *via* 3-bromo-1-aza*meso*benzanthrone (V; R = Br). In the alkaline fusion of 1-aza*meso*benzanthrone (V; R = H), 9 : 18-diaza*iso*violanthrone (I) was again obtained and not the expected 15 : 18-diazaviolanthrone (II).

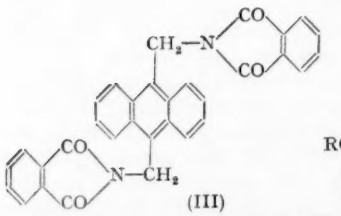
9 : 10-BISPHTHALIMIDOMETHYLANTHRACENE (III) was prepared by treatment of anthracene with *N*-chloromethylphthalimide (Buc, *J. Amer. Chem. Soc.*, 1947, **69**, 254; Sakellarios, *ibid.*, 1948, **70**, 2822) and a trace of zinc chloride in nitrobenzene as in G.P. **442,774** (the product was not characterised in the patent) or alternatively by employing aluminium chloride in carbon disulphide. Degradative oxidation of (III) to anthraquinone established the positions of the side chains.

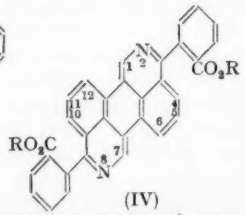
From the fusion of 9 : 10-bisphthalimidomethylanthracene with a mixture of aluminium chloride and sodium chloride, 3 : 9-diphenyl-2 : 8-diazaperylene-2′ : 2″-dicarboxylic acid (IV; R = H) was obtained, as its dihydrochloride dihydrate, and further characterised by conversion into the diethyl ester (IV; R = Et), which was found to be homogeneous by the formation of only one band on chromatography of its nitrobenzene solution on alumina. The above method was based on the conditions used by Ebel for the preparation of 1-phenyl*iso*quinoline-2′-carboxylic acid (G.P. **614,196**).

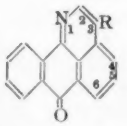
The final cyclisation of (IV; R = H) to 9 : 18-diaza*iso*violanthrone was carried out in fuming sulphuric acid at 100° and gave an alkali-soluble product. This, on sublimation at low pressure, gave the dye (I), insoluble in alkali but soluble in hot alkaline sodium dithionite solution, giving a deep blue vat from which cotton was dyed violet. The cyclisation was also brought about by phosphoric oxide in polyphosphoric acid without the formation of an alkali-soluble intermediate.

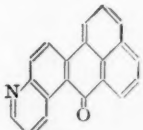

(I)


(II)


(III)


(IV)


(V)


(VI)

The dye was shown to be (I) by the identity of its ultra-violet and visible absorption spectra with those of the dye from the potassium hydroxide fusion of 3-bromo-1-aza*meso*benzanthrone (V; R = Br), obtained by direct bromination of 1-aza*meso*benzanthrone (G.P. 627,258). The position of the bromine atom has been established by degradative oxidation of the bromo-1-aza*meso*benzanthrone to anthraquinone-1-carboxylic acid. This showed that the bromine atom was in the pyridine ring, presumably in the expected 3-position because of the absence of bromine in the product from the fusion.

1-Aza*meso*benzanthrone (V; R = H) on potassium hydroxide fusion at 260—280° also gave 9 : 18-diaza*iso*violanthrone (I), no violanthrone isomer (II) being detected. The alkaline fusion of *meso*benzanthrone at temperatures above 220° gave no *iso*violanthrone (Lüttringhaus and Neresheimer, *Annalen*, 1929, **473**, 283), whereas alkaline fusion of

pyridino(3′ : 2′-8 : 9)*meso*benzanthrone (VI) has been shown by Bradley and Sutcliffe (*J.*, 1952, 2118) to lead to an *iso*violanthrone-type structure for cyananthrene. There may be some correlation between the method of cyclisation to *iso*violanthrone-type structures and the possession of heterocyclic nitrogen atoms.

Di-1-aza*meso*benzanthronyl (possibly the 4 : 4′-compound) obtained by the low-temperature alkaline fusion of 1-aza*meso*benzanthrone (cf. G.P. 627,258) was fused with alkali at a higher temperature and then gave (I).

Experimental

9 : 10-*Bisphthalimidomethylanthracene* (III).—(*a*) *N*-Chloromethylphthalimide (8 g.), anthracene (3·8 g.), freshly sublimed aluminium chloride (5 g.), and carbon disulphide (50 c.c.) were refluxed until no further hydrogen chloride was evolved (about 8 hr.), stirring being continued as long as possible. The carbon disulphide was then distilled off, and ice (*ca.* 100 g.) and concentrated hydrochloric acid (20 c.c.) were added. After decomposition the mixture was filtered and the precipitate washed with water. The 9 : 10-*bisphthalimidomethylanthracene* crystallised from *m*-cresol as yellow needles (1·15 g.), m. p. >360° (Found : C, 77·1; H, 4·0; N, 6·0. $C_{32}H_{20}O_4N_2$ requires C, 77·4; H, 4·1; N, 5·6%).

(*b*) (cf. G.P. 442,774) *N*-Chloromethylphthalimide (24 g.), anthracene (11·4 g.), and fused zinc chloride (1·3 g.) were heated at 100° in redistilled nitrobenzene (75 c.c.) with stirring for 8 hr. The mixture was cooled and filtered and the solid washed thoroughly with benzene. The crude yellow product (10·9 g.) was satisfactory for the next stage of the synthesis and crystallised from *m*-cresol in yellow needles identical with the above (Found : C, 77·2; H, 4·0%).

Oxidation of 9 : 10-*Bisphthalimidomethylanthracene* (III).—A suspension of 9 : 10-bisphthalimidomethylanthracene (1 g.) in acetic acid (20 c.c.) was refluxed during the addition of chromium trioxide (6 g.) in water (6 c.c.) and for a further 6 hr. Water was added and, after standing, the solid (0·40 g.) was filtered off, washed, dried, and crystallised from acetic acid. The anthraquinone obtained had m. p. 285° and was not depressed on admixture with an authentic specimen.

3 : 9-*Diphenyl*-2 : 8-*diazaperylene*-2′ : 2″-*dicarboxylic Acid* (IV; R = H).—Freshly sublimed aluminium chloride (43 g.) and sodium chloride (8·6 g.) were heated at 130—140° and 9 : 10-bisphthalimidomethylanthracene (8·6 g.) added with stirring. The temperature was maintained for 8 hr. and the cooled mass, after decomposition by the addition of ice, was extracted with hot hydrochloric acid (10%; 4 × 100 c.c.). 3 : 9-*Diphenyl*-2 : 8-*diazaperylene*-2′ : 2″-*dicarboxylic acid dihydrochloride dihydrate* (2·48 g.) separated as orange needles, which were dried at room temperature under vacuum (Found : C, 63·9; H, 4·5. $C_{32}H_{18}O_4N_2,2HCl,2H_2O$ requires C, 63·7; H, 4·0%). Analyses showed that drying at higher temperatures led to products of indefinite composition with loss of water and hydrogen chloride.

The mother-liquors of the product were heated to the b. p., aqueous ammonia was added to precipitate the aluminium hydroxide, the whole was filtered, the residue was extracted with boiling water containing a little aqueous ammonia and filtered, and the filtrates were evaporated to *ca.* 100 c.c., to give the free base (0·05 g.), m. p. >360°.

The above dihydrochloride dihydrate was dried on the water-bath, and the product (1·0 g.) was refluxed for 1 hr. with thionyl chloride (10 c.c.). The excess of thionyl chloride was removed under vacuum, and the product refluxed for 2 hr. with ethanol (20 c.c.). Ethanol was removed and the solid extracted twice with hot sodium carbonate solution, filtered, washed, and dried, to give *diethyl* 3 : 9-*diphenyl*-2 : 8-*diazaperylene*-2′ : 2″-*dicarboxylate* (0·94 g.), which crystallised from nitrobenzene in yellow needles, m. p. 276° (Found : C, 78·5; H, 4·9; N, 4·9. $C_{36}H_{26}O_4N_2$ requires C, 78·5; H, 4·8; N, 5·1%).

3-*Bromo*-1-*aza*meso*benzanthrone* (cf. G.P. 627,258).—1-Aza*meso*benzanthrone (2·2 g.), nitrobenzene (65 c.c.), bromine (3·5 c.c.), and iodine (0·02 g.) were refluxed for 5 hr. On cooling, crystals of 3-bromo-1-aza*meso*benzanthrone (2·7 g., 91%) separated. These were filtered off, washed with benzene, dried, and recrystallised from nitrobenzene as yellow needles, m. p. 256° (Found : C, 62·0; H, 2·7; Br, 26·2. Calc. for $C_{16}H_8ONBr$: C, 62·0; H, 2·6; Br, 25·8%).

Oxidation of 3-*Bromo*-1-*aza*meso*benzanthrone*.—3-Bromo-1-aza*meso*benzanthrone (1·0 g.), chromium trioxide (1·62 g.), and glacial acetic acid (40 c.c.) were refluxed for 6 hr. On cooling, unchanged 3-bromo-1-aza*meso*benzanthrone (0·03 g.) separated and was filtered off. The filtrate was diluted with water (100 c.c.) and evaporated to 20 c.c. twice, and acidified with hydrochloric acid, and the precipitated acid was filtered off and purified by acidification of its

soluble ammonium salt. The acid was converted through its acid chloride into ethyl anthraquinone-1-carboxylate, m. p. 167°, admixture with an authentic specimen giving no depression.

*Di-1-aza*mesobenzanthronyl (*possibly the* 4 : 4′-*isomer*) (cf. G.P. 627,258).—1-Aza*meso*benzanthrone (1·0 g.), ethanol (15 c.c.), and finely ground potassium hydroxide (10 g.) were heated at 110—120° in a nickel crucible with occasional stirring. The mixture rapidly became dark green, and after 1 hr. was diluted with water (50 c.c.), and excess of hydrogen peroxide solution (20-vol.) gradually added to oxidise any reduced material. After filtration and drying, the product was extracted for 6 hr. in a Soxhlet extractor with ethanol to remove unchanged 1-aza*meso*benzanthrone. The residue (0·75 g.) was twice sublimed at 400°/10^{-3} mm. Di-1-aza*meso*benzanthronyl was obtained as an orange-brown product, m. p. >360°, which was slightly soluble on boiling with sodium dithionite and dilute sodium hydroxide solution (Found : C, 83·6; H, 3·2. Calc. for $C_{32}H_{16}O_2N_2$: C, 83·5; H, 3·5%).

9 : 18-*Diaza*isoviolanthrone (I).—(*a*) Dried 3 : 9-diphenyl-2 : 8-diazaperylene-2′ : 2″-dicarboxylic acid hydrochloride (0·72 g.) and fuming sulphuric acid (23% of SO_3; 10 c.c.) were heated at 100° for 2½ hr. The mixture was poured on ice (75 g.), and the precipitate filtered off and washed with water. The dry product (0·51 g.), which was soluble in sodium hydroxide solution, was sublimed at 450°/10^{-3} mm. with considerable charring. 9 : 18-*Diaza*isoviolanthrone (0·18 g.) was obtained as fine purple needles, with a strong green reflex, and was insoluble in sodium hydroxide solution. It dissolved in hot dilute sodium hydroxide solution containing sodium dithionite, giving an intense blue vat which was filtered; the dye was reprecipitated from the filtrate by the passage of air or by the gradual addition of hydrogen peroxide solution (20-vol.). The product after being filtered, washed, and dried was resublimed as before (Found : C, 83·2; H, 3·4; N, 6·2. $C_{32}H_{14}O_2N_2$ requires C, 83·8; H, 3·1; N, 6·1%). A portion of the dye was converted into its vat and chromatographed, on a 40-cm. alumina column jacketed with carbon tetrachloride vapour; sodium hydroxide solution (2%) containing a little sodium dithionite was used as eluent. Only one band was observed. The ultra-violet and visible absorption spectra of the dye were determined in concentrated sulphuric acid, the dye being insoluble in all the usual organic solvents [light absorption : Max., 2500 (ε 3·95 × 10^4), 2930 (ε 3·52 × 10^4) and 6630 Å (ε 4·97 × 10^4); Min., 2790 Å (ε 3·18 × 10^4)]. The determinations were made by means of a Unicam S.P. 500 quartz spectrophotometer (kindly lent by the Wool Textile Research Council).

(*b*) The above dihydrochloride dihydrate (0·2 g.), phosphoric oxide (1·0 g.), and phosphoric acid (10 g., previously heated at 250° for 3 hr.) were heated with stirring for 3 hr. at 250—260°. The product was cooled and made alkaline with sodium hydroxide, sodium dithionite added, and the solution boiled and filtered. The hot filtrate was oxidised with hydrogen peroxide, and filtered after settling. The dye (0·08 g.) was purified as above and identified by its spectrum, this method also being used in the following three experiments.

(*c*) 1-Aza*meso*benzanthrone (0·5 g.), finely ground potassium hydroxide (4·5 g.), and anhydrous potassium acetate (0·5 g.) were heated at 240—250° for 1 hr. with stirring in a nickel crucible set in an iron block. The mixture was cooled, then diluted with water (50 c.c.), and hydrogen peroxide solution was gradually added. The precipitated dye was filtered off and the dry residue (0·48 g.) was extracted for 6 hr. in a Soxhlet extractor with ethanol to remove unchanged starting material. The dye (0·30 g.) was further purified as above (Found : C, 84·1; H, 3·2%) and, as before, only one band was obtained on the column.

(*d*) 3-Bromo-1-aza*meso*benzanthrone (0·45 g.), finely ground potassium hydroxide (4·5 g.), and anhydrous potassium acetate (0·5 g.) were heated at 260—270° for 1 hr. The dye (0·25 g.) was isolated as described above and chromatography failed to reveal the presence of more than one compound.

(*e*) 4 : 4′-Di-1-aza*meso*benzanthronyl (0·2 g.), finely ground potassium hydroxide (4·5 g.), and anhydrous potassium acetate (0·5 g.) were heated at 260—280° for 1 hr. to give the dye (0·11 g.) as above.

The authors thank the Huddersfield Education Committee for the award of the Joseph Blamires Research Scholarship, the Department of Scientific and Industrial Research for a maintenance allowance to one of them (J. K.) and Mr. E. Coates for supervision of the spectrographic determinations.

Huddersfield Technical College. [*Received, November 3rd,* 1953.]

Organosilicon Compounds. Part VIII. The (Trimethylsilylmethyl)-benzoic Acids.*

By C. Eaborn and S. H. Parker.

[Reprint Order No. 4775.]

The apparent ionisation constants in 50% water–ethanol and the absorption spectra of the three (trimethylsilylmethyl)benzoic acids are reported and discussed.

Studies of the electronic influence of the trimethylsilyl group attached directly to an aromatic nucleus have shown that an important $-E$ effect opposes the expected $+I$ effect of the group (Benkeser and Krysiak, *J. Amer. Chem. Soc.*, 1953, **75**, 2421; Speier, *ibid.*, p. 2930; Roberts and Regan, *ibid.*, p. 4102; Roberts, McElhill, and Armstrong, *ibid.*, 1949, **71**, 2923). With a methylene group between the silicon atom and the nucleus the $+I$ effect must be reduced, but the $-E$ effect is eliminated, and the strengths of the (trimethylsilylmethyl)benzoic acids reveal the overall result. The apparent ionization constants of these acids in 50% ethanol–water at 18° are shown in the following Table, along with those for benzoic acid and unsubstituted toluic acids determined with the same apparatus. The "pK_a" values listed are actually the values of the pH at half neutralization, and are subject to a standard deviation of $\pm 0{\cdot}03$.

R(in R·C_6H_4·CO_2H)	H	*o*-CH_3	*o*-$Me_3Si{\cdot}CH_2$	*m*-CH_3	*m*-$Me_3Si{\cdot}CH_2$	*p*-CH_3	*p*-$Me_3Si{\cdot}CH_2$
pK_a	5·70	5·70	6·34	5·77	6·00	5·88	6·08
10^6K_a	2·00	2·00	0·457	1·70	1·00	1·32	0·832

The most striking features of the Table are: (i) the strong electron supply from the trimethylsilylmethyl group [use of Roberts, McElhill, and Armstrong's value (*loc. cit.*) of 1·464 for the Hammett rho constant for acid dissociation in the medium at 25° leads to σ_p and σ_m values for the group of $-0{\cdot}260$ and $-0{\cdot}205$ respectively—compare $\sigma_p = -0{\cdot}268$ for the *p*-methoxy-group]; (ii) the relatively small difference between the effects of the group in the *meta*- and *para*-positions; (iii) the decrease in acid strength caused by the group in the *ortho*-position, surprisingly large in view of the existing generalization that all *ortho*-substituents increase the strength of benzoic acid (see Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p. 743). The facts are consistent with the operation of a large $+I$ effect from the silicon atom, particularly since the effect of replacing a methyl-hydrogen atom by the trimethylsilyl group falls off in the order $o > m > p$ (cf. Roberts, Clements, and Drysdale, *J. Amer. Chem. Soc.*, 1951, **73**, 2181). In *o*-(trimethylsilylmethyl)benzoic acid the $+I$ effect presumably operates so strongly that it outweighs the acid-strengthening steric effects which normally predominate for *ortho*-substitution. This strong electron supply to the *ortho*-position accounts also for the large proportion of *ortho*-substitution (~80% of products isolated) on nitration of benzyltrimethylsilane with copper nitrate in acetic acid (Benkeser and Brumfield, *ibid.*, p. 4770) or nitric acid in acetic anhydride (Eaborn and Parker, unpublished work).

Substitution of the trimethylsilyl group for a methyl-hydrogen atom in the toluic acids causes a bathochromic shift of the main (~235) maximum in all cases, but the shift is much greater for the *para*-acids, as the Table shows. Thus the silyl group in this position supplies electrons strongly, and by a delocalization rather than an inductive mechanism (Doub and Vandenbelt, *ibid.*, 1947, **69**, 2714; Crawford, *J.*, 1953, 2061), suggesting contributions from structures such as $Me_3Si^+ CH_2{=}\langle\rangle{=}C{<}^{O^-}_{OH}$ in the excited state. This effect could not operate from the *meta*-position and would be sterically inhibited in the *ortho*-position.

Co-ordination of carbonyl oxygen to silicon would be geometrically easy in *o*-(trimethylsilylmethyl)benzoic acid. The absence of any unusual feature in the absorption

* Part VII, *J.*, 1953, 4154.

spectrum indicates that such co-ordination (which would be analogous to the chelation suggested by Benkeser and Brumfield, *loc. cit.*, for trimethyl-*o*-nitrobenzylsilane) is not significant. The low ionization constant of the acid supports this, since the co-ordination

Values of $\lambda_{max.}$ *(in mμ) for acids* $R{\cdot}C_6H_4{\cdot}CO_2H$, *with corresponding values of log ε in parentheses.*

R	*o*-Me	*o*-$Me_3Si{\cdot}CH_2$	*m*-Me	*m*-$Me_3Si{\cdot}CH_2$	*p*-Me	*p*-$Me_3Si{\cdot}CH_2$
In hexane	205 (4·12)	210·5 (4·55)	206 (4·09)	210·5 (4·48)	<206	208·5 (4·17)
	234·7 (4·06)	238·5 (3·96)	235·5 (4·10)	239 (4·02)	240·5 (4·19)	256·5 (4·29)
	282 (3·22)	295·5 (3·45)	281 (3·15)	290·5 (3·23)	272 (3·02)	~270 *
	~290 *	—	291 (3·08)	—	283·2 (2·88)	—
In methanolic HCl	229 (3·92)	232·5 (3·91)	231·5 (4·03)	232 (3·95)	237·5 (4·15)	252·5 (4·26)
	279 (3·09)	290 (3·35)	286 (3·02)	289 (3·17)	281·5 (2·77)	—
	—	208 (4·6)	—	211 (4·5)	—	—

* Signifies a point of inflexion.

would be acid-strengthening; Sommer, Gold, Goldberg, and Marans (*J. Amer. Chem. Soc.*, 1949, **71**, 1509) took the lowered strength of trimethylsilyl-substituted aliphatic acids to signify the absence of co-ordination.

Experimental

M. p.s and b. p.s are corrected.

m-*Chlorobenzyl Bromide.*—*m*-Chlorotoluene was brominated by Barnes and Gordon's method for *o*-chlorotoluene (*ibid.*, p. 2644) to give *m*-chlorobenzyl bromide (61%), b. p. 122—124°/19 mm.

(*Chlorobenzyl*)*trimethylsilanes.*—Chlorotrimethylsilane (1·1 moles) and the Grignard reagent from 1 mole of *o*- or *p*-chlorobenzyl chloride or *m*-chlorobenzyl bromide in ether (600 ml.) were boiled under reflux for 8 hr. Aqueous sulphuric acid was added until two clear layers separated and the ethereal layer was washed, dried (Na_2SO_4), and fractionated, to give ~60% yields of o-, b. p. 222—223°, n_D^{20} 1·5128 (Found: C, 60·5; H, 7·8. $C_{10}H_{15}ClSi$ requires C, 60·4; H, 7·6%), p-, b. p. 231—232°, n_D^{19} 1·5154 (Found: C, 60·7; H, 7·8%), and m-*chlorobenzyltrimethylsilane*, b. p. 228—229°, n_D^{20} 1·5108 (Found: C, 60·4; H, 7·6%).

(*Trimethylsilylmethyl*)*benzoic Acids.*—The lithium aryl from the chlorobenzyltrimethylsilane in ether was poured on solid carbon dioxide. When the mixture had warmed to room temperature dilute sulphuric acid was added until two clear layers separated. The ethereal layer was repeatedly extracted with 0·2N-aqueous sodium hydroxide, the extracts being immediately added to excess of aqueous hydrochloric acid. The organic acid was extracted with ether, and recovered by evaporation of the solvent. There were obtained in 75—85% yield: o-(*trimethylsilylmethyl*)*benzoic acid*, m. p. 77·5° (from aqueous ethanol) (Found: C, 63·4; H, 7·7. $C_{11}H_{16}O_2Si$ requires C, 63·4; H, 7·7%) [*anilide*, m. p. 113° (Found: C, 72·3; H, 7·7; N, 4·8. $C_{17}H_{21}ONSi$ requires C, 72·1; H, 7·5; N, 4·95%)]; the m-*acid*, m. p. 96·5° (from light petroleum) (Found: C, 63·3; H, 7·6%) [*anilide*, m. p. 111·4° (Found: C, 72·3; H, 7·5; N, 4·8%)]; and the p-*acid*, m. p. 179° (from acetone–light petroleum) (Found: C, 63·5; H, 7·8%) [*anilide*, m. p. 137·4° (Found: C, 71·7; H, 7·6; N, 5·2%)]. Anilides were recrystallized from light petroleum.

The structures of the acids were confirmed by boiling them with N-aqueous sodium hydroxide, the expected toluic acids being obtained.

Determination of Apparent Ionization Constants.—Roberts and Regan's method (*loc. cit.*) was used, except that a Marconi-Ekco T.F.511C pH meter was employed, and the temperature was 18° ± 0·5°. The same assumptions are made in calculating the apparent ionization constants.

Absorption Spectra.—A Unicam S.P.500 spectrophotometer was employed. In hexane, the value of $\varepsilon_{max.}$ of the toluic acids and their trimethylsilyl derivatives at the ~235 maxima departed markedly from Beer's law below 10^{-4}M.

"Methanolic hydrochloric acid" was prepared by adding 10 vol. % of 11N-aqueous hydrochloric acid to methanol.

The following spectral data are not listed above.

Acids in aqueous alkali. The molar ratio of alkali to acid was *ca.* 3 : 1, and the spectra are probably those of the carboxylate ions; Doub and Vandenbilt (*loc. cit.*) give $\lambda_{max.}$ = 235 mμ for the *p*-toluate ion in water. The *ortho*-compounds have ill-defined inflexions at ~230 mμ (log ε ~4·2) probably corresponding to the maxima of the other isomers in this region.

R (in $R{\cdot}C_6H_4{\cdot}CO_2H$)	*o*-Me		*o*-$Me_3Si{\cdot}CH_2$		*m*-Me			*m*-$Me_3Si{\cdot}CH_2$			*p*-Me	*p*-$Me_3Si{\cdot}CH_2$
$10^4 \times$ [NaOH], N	160	160	2·4	160	2·4	120	120	1·2	1	120	2·4	2·4
$\lambda_{max.}$, mμ	262·5	270	205	277·7	229·5	275·5	~283 *	206	230 *	284	235	250
log $\varepsilon_{max.}$	2·64	2·61	4·42	2·97	3·83	2·90	—	4·54	(3·9)	3·03	4·03	4·21

* Denotes inflexion.

Anilides in aqueous methanol. The *ortho*-compounds were examined in 3 vol. % water in methanol, the others in 32 vol. % water in methanol. The spectra of the *meta*-compounds coincide at 250—278 mμ.

R (in $R{\cdot}C_6H_4{\cdot}CO{\cdot}NHPh$)	*o*-Me	*o*-$Me_3Si{\cdot}CH_2$	*m*-Me	*m*-$Me_3Si{\cdot}CH_2$	*p*-Me	*p*-$Me_3Si{\cdot}CH_2$
$\lambda_{max.}$, mμ	250·5	253	263·5	263·5	265	270
$\varepsilon_{max.}$	4·19	4·16	4·11	4·11	4·21	4·32

A grant from the Research Fund of the Chemical Society is gratefully acknowledged.

UNIVERSITY COLLEGE, LEICESTER. [*Received, November 9th*, 1953.]

The Effect of Dissolved Oxygen on Diamagnetic Susceptibilities.

By B. C. EGGLESTON, D. F. EVANS, and R. E. RICHARDS.

[Reprint Order No. 4787.]

It is shown that oxygen exerts its normal paramagnetism when dissolved in benzene and in heptane, and the true susceptibilities of these liquids are changed by about 4·5% and 8·5% respectively when they are saturated with oxygen. This effect has been overlooked by earlier workers, probably because the liquids take up atmospheric oxygen very rapidly. This is demonstrated for the particular case of toluene by spectrophotometric measurements. Diamagnetic susceptibilities of organic liquids saturated with air may therefore be in error by as much as 1·7%. Two types of Gouy tubes are described, which can be evacuated, and are suitable for use with organic liquids.

IN the determination of diamagnetic susceptibilities of organic liquids, little attention appears to have been given to the effect of dissolved atmospheric oxygen, although many workers have used boiled-out distilled water for calibration. The solubility of oxygen in water is much less than in the majority of organic liquids (Seidell, " Solubility of Inorganic and Metal Organic Compounds," Van Nostrand, 1940). Broersma (*J. Chem. Phys.*, 1949, **17**, 873), who alone appears to have studied this effect experimentally, says " The presence of paramagnetic oxygen is also of great interest. For water differences up to 3 per mil were found, after boiling for some time. Hydrocarbons never showed differences larger than our precision of measurement (~ 0·1%) in this respect." However, from the recorded solubilities of oxygen, and from its paramagnetic susceptibility, it can be calculated that the expected effect is only 0·14% of the diamagnetic susceptibility for water at room temperature, but should be approximately 1% for benzene and as much as 1·7% for heptane at room temperature (Seidell, *op. cit.*). These effects are much greater than the probable error of Broersma's and other recent measurements of diamagnetic susceptibilities. It is unlikely that oxygen dissolved in organic liquids would fail to exert its normal paramagnetism, especially as it appears to behave normally in its clathrate compound with β-quinol (Evans and Richards, *J.*, 1952, 3295) and also in very dilute solutions in liquid nitrogen (Perrier and Onnes, *Leiden Communications*, **139**, *d*, 48). Experiments have therefore been made on the effect of dissolved oxygen on the susceptibilities of benzene and *n*-heptane, completely air-tight Gouy tubes being used.

EXPERIMENTAL

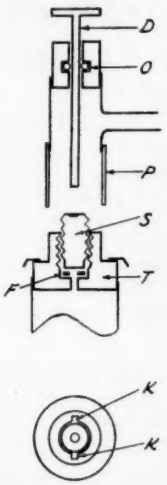
The susceptibilities of the liquids were measured by the Gouy method using the apparatus described by Evans and Richards (*loc. cit.*). It is required that the Gouy tubes should have a vacuum-tight seal which will withstand organic solvents when the tube is shaken to ensure

complete saturation of the liquid with the gas used. Attempts to use ground-glass connections of suitable size and shape failed, largely owing to the poor lubricating quality of greases which are unaffected by organic solvents. Two other designs were therefore used. The first, which was satisfactory for heptane, is illustrated in Fig. 1. The Gouy tube is made from egg-shell (0·3 mm. thick) glass tubing, and is cemented with Bakelite varnish to a brass cylinder, *D*; This contains an O-ring vacuum seal (Kurie, *Rev. Sci. Instr.*, 1948, **19**, 485) through which passes a glass tube, *G*, sealed at the lower end and with a small hole, *H*, blown in the side. Small copper suspension hooks are soldered at the top of the cylinder. By raising and lowering the glass tube, *G*, the Gouy tube can be sealed or opened to a gas system connected to the top of *G*.

This tube proved unsatisfactory for benzene, because the rubber O-ring swelled when in contact with the liquid. A somewhat more complicated arrangement was therefore used as illustrated in Fig. 2. The egg-shell Gouy tube is cemented with cold-setting Araldite to a brass top *T*, which supports the copper suspension hooks. A central hole in the brass top may be closed or opened by the screw, *S*, which forms a vacuum-tight seal when screwed down against the thin annular washer, *F*, which is made of "Fluon" (polytetrafluoroethylene). When the screw is released, gases may pass in or out of the Gouy tube through the slots, *K*, in the outer

FIG. 1.

FIG. 2.



screw thread. The brass top, *T*, can be connected to a vacuum system by means of a short length of transparent plastic tubing, *P*, and the sealing screw, *S*, is operated by a stainless-steel screwdriver, *D*, which passes through the O-ring seal, *O*.

For each sample, the magnetic force was measured after saturation with (*a*) air, (*b*) nitrogen, and (*c*) oxygen. The liquids were degassed either by repeatedly cooling them to −78° and evacuating the Gouy tube (*n*-heptane) or by repeatedly opening the Gouy tube briefly to an evacuated bulb, and shaking vigorously each time after closing the seal (benzene). After this, the samples were saturated with the nitrogen or oxygen at atmospheric pressure, with frequent shaking between each exposure. Measurements were made at 21·5° ± 1°.

Materials.—The *n*-heptane was a pure sample prepared synthetically, which was kindly lent by Dr. F. J. Stubbs.

A sample of Kahlbaum's benzene "for molecular weight determinations" was fractionally distilled, and the middle fraction, boiling over a range of 0·2°, was collected. The oxygen and nitrogen were obtained from commercial cylinders.

Results.—The apparatus was calibrated with air-saturated benzene, the susceptibility of which was assumed to be $-0{\cdot}7020 \times 10^{-6}$ (Angus and Tilston, *Trans. Faraday Soc.*, 1947, **43**, 235; Selwood *et al.*, *J. Amer. Chem. Soc.*, 1939, **61**, 3168; 1940, **62**, 2765, 3055). The values for the diamagnetic susceptibility, χ, of heptane are given in Table 1. The value found for the ratio of the susceptibilities of air-saturated heptane to air-saturated benzene agrees exactly with that found by Broersma (*loc. cit.*), but the ratio for the de-oxygenated liquids differs by about 1%.

TABLE 1. *Susceptibilities of heptane.**

Saturated with :	$-10^6\chi$	$-10^6\chi_M$	Saturated with :	$-10^6\chi$	$-10^6\chi_M$	Saturated with :	$-10^6\chi$	$-10^6\chi_M$
nitrogen	0·8665	86·65	air	0·8513	85·13	oxygen	0·7944	79·44

TABLE 2. *Susceptibilities of benzene.**

Saturated with :	$-10^6\chi$	$-10^6\chi_M$	Saturated with :	$-10^6\chi$	$-10^6\chi_M$	Saturated with :	$-10^6\chi$	$-10^6\chi_M$
itrogen	0·7081	55·22	air	0·7020 †	54·76	oxygen	0·6756	52·70

* χ = Specific susceptibility; χ_M = molar susceptibility. † Assumed.

DISCUSSION

It is clear from the above results that oxygen exerts a paramagnetic effect when dissolved in these solvents. In the case of heptane, the change of susceptibility on removal of dissolved *air* is $1{\cdot}7_9\%$, in good agreement with the value of 1·73% calculated from the Bunsen coefficient, α, for oxygen in heptane of 0·332 at 20°, reported by Glendinning and Bedwell (" Solubility of atmospheric gases, hydrogen and carbon monoxide," Unpublished Ministry of Supply Report), and the paramagnetic susceptibility of gaseous oxygen at 21·5° ($+106 \times 10^{-6}$; Burris and Hause, *J. Chem. Phys.*, 1943, **11**, 442). Furthermore, using the value of the susceptibility of *n*-heptane saturated with oxygen, and allowing for the impurities in cylinder oxygen (about 2%), we calculate a value for the susceptibility of dissolved oxygen at 21·5° of $+111 \times 10^{-6}$. This compares favourably with the value for gaseous oxygen at this temperature of 106×10^{-6}.

The change of susceptibility of benzene on removal of dissolved air is 0·87%, compared with the calculated value of 0·96%, using a value for the Bunsen coefficient α for oxygen in benzene at 20° of 0·206. This is an average of the values quoted by Glendinning and Bedwell (0·207) (*loc. cit.*) and by Horiuti (0·204) (*Sci. Papers Inst. Phys. Chem. Res., Tokyo*, 1931, **17**, 125.) From the measurements on benzene saturated with oxygen, a value for the paramagnetic susceptibility of oxygen at 21·5° is obtained of 110×10^{-6}.

From these two examples, it seems likely that dissolved oxygen exerts its usual paramagnetism in organic solvents. The failure of Broersma (*loc. cit.*) to observe any effect of this kind is probably due to the great rapidity with which these substances appear to take up oxygen from the air. This was shown qualitatively, by using the absorption band in the near ultra-violet region of the spectrum, which is shown by oxygen in aromatic solvents (Evans, *J.*, 1953, 345). Quartz absorption cells of thickness 1 cm., fitted with C 10 sockets, were filled with toluene, which was degassed and then saturated with nitrogen. One cell was then opened to the air, and the increase in optical density at 2850 Å observed on a Unicam SP 500 spectrophotometer, without moving the cells in any way. After 10 min. the optical density was about 40% of that corresponding to complete saturation with air, and after 20 min. about 70% of that value. The effect of shaking was particularly marked. If the toluene saturated with nitrogen was poured quickly into another absorption cell, its optical density measured immediately was already 65% of that expected for complete saturation with air. During the measurement of diamagnetic susceptibilities the samples are often exposed to the air for much longer periods than these, and so complete saturation would presumably be obtained, even if the sample had been previously degassed.

It seems likely, therefore, that many measurements of diamagnetic susceptibilities reported in the past are in error by an amount corresponding to the effect of dissolved oxygen, which may be as great as 1·7%. Since there are few recorded values for the solubility of oxygen in organic liquids, it is clearly desirable that accurate measurements of susceptibilities should be made in the absence of air.

We thank Imperial Chemical Industries Limited for a Research Fellowship (D. F. E.). We are also grateful to Professor W. F. K. Wynne-Jones for drawing our attention to the work of Glendinning and Bedwell, and to the Ministry of Supply for permission to use the results.

THE PHYSICAL CHEMISTRY LABORATORY,
SOUTH PARKS ROAD, OXFORD.

[*Received, November 11th*, 1953.]

The Photochemical Autoxidation of iso*Propylbenzene.*

By H. W. Melville and S. Richards.

[Reprint Order No. 4673.]

The hydroperoxidation of liquid *iso*propylbenzene is a chain reaction which can be initiated by the free radicals produced from azonitriles by thermal decomposition or by irradiation with light in the near ultra-violet.

The course of the reaction has been followed by measurement of the oxygen absorbed, by means of an automatically controlled manostat.

The kinetics of the reaction show that the chains are propagated by the cycle

$$R\cdot + O_2 \longrightarrow RO_2\cdot$$

$$RO_2\cdot + RH \longrightarrow RO_2H + R$$

where R is a free radical $C_6H_5\cdot CMe_2\cdot$. With oxygen pressures above 200 mm. the first of these reactions is fast and the rate is controlled by the second of them. Termination is by removal of peroxy-radicals by a second-order reaction.

The rate of production of free radicals during the autoxidation has been obtained from the rate at which the sensitiser evolves nitrogen when under irradiation. The life-time of the reaction chains has been determined by the use of intermittent light. These data enable the rate coefficients for the rate-controlling propagation and termination steps to be obtained.

It has previously been observed that when *iso*propylbenzene is shaken at 85° with dry oxygen under irradiation from a mercury-vapour lamp oxygen is slowly taken up and a hydroperoxide is formed (Hock and Lang, *Ber.*, 1944, **77**, 257). The reaction occurring was sown to be $C_6H_5\cdot CHMe_2 + O_2 \longrightarrow C_6H_5\cdot CMe_2\cdot O\cdot OH$, and the yield of peroxide, based on the oxygen absorbed, was almost quantitative.

Other workers (Armstrong, Hall, and Quin, *J.*, 1950, 130, 666) have shown that a similar reaction occurs when oxygen is passed through an aqueous emulsion of *iso*propylbenzene at 85°. Preliminary investigation of the kinetics of the reaction occurring under these conditions indicated that it was similar to other autoxidations, such as those of olefins, aldehydes, and tetralin, which were known to proceed by free-radical chain mechanisms.

It has been found for several other substances that the mechanism of thermal and photochemical autoxidation differs only in the method by which chains are initiated. It therefore seemed likely that photochemical autoxidation of *iso*propylbenzene would proceed by the mechanism common to the other substances studied, and that the methods used to determine their rate coefficients would be applicable also to *iso*propylbenzene.

The direct photo-oxidation is, however, not suitable for this type of study, as the absorption spectrum of *iso*propylbenzene shows that intense light absorption would occur and the distribution of free radicals in a reaction vessel would probably not be uniform. For this reason azonitriles were used as photosensitisers. These have the additional advantages that they absorb in spectral regions which are readily accessible and do not seem to undergo a decomposition by free-radical attack, which would complicate the kinetics.

Experimental

The apparatus used was, in most respects, similar to that used by Melville and Cooper (*J.*, 1951, 1984) for studying the autoxidation of decanal. A mercury diffusion pump, backed by an oil-pump, was used to evacuate the system, which was provided with liquid-air traps, manometers, oil-trap, safety-valve, and storage bulbs for oxygen and nitrogen. The manostat was the same as in Melville and Cooper's Fig. 2, but without the refilling devices. The dibutyl phthalate was replaced by silicone oil. The thermionic relay was that described by Bolland (*Proc. Roy. Soc.*, 1946, *A*, **186**, 218) but the Sunvic hot-wire switch was replaced by a magnetic switch. The manostat was immersed as completely as possible in a water thermostat maintained at 25° ± 0·1° by means of an A.C. thyratron relay operated by a mercury–toluene regulator.

In the present work the oxidation was carried out at temperatures up to 80°; for this reason a reaction vessel of Pyrex glass was used which incorporated a condenser through which tap water could be circulated.

The connection from the reaction vessel to the manostat was through a standard B10 Quickfit joint and a glass spiral of 2-mm. tubing. The spiral consisted of about 6 coils, each about 2 inches in diameter. This is flexible enough to permit vigorous shaking, which was effected by connecting an elliptical wheel through a metal rod and flexible connection to a screw clip on the socket at the end of the spiral. The axle carrying the elliptical wheel was connected by gears to a small electric stirring motor. The motor was generally run at high speeds and geared down to provide about 300—400 shaking cycles per min. The required range of shaking speeds (100—600 cycles per min.) could be obtained by altering the motor speed.

The reaction vessel was in a separate thermostat (a 4-l. Pyrex beaker) maintained within $\pm 0{\cdot}05°$ of the required temperature by means of a mercury–xylene regulator and a Sunvic hot-wire vacuum switch.

It is necessary to evacuate the system before filling it with oxygen. As *iso*propylbenzene is fairly volatile, it was necessary to freeze it in liquid air during the evacuation. For this reason it was arranged that the 4-l. beaker could be lowered clear of the reaction vessel.

The ultra-violet-lamp housing was placed in front of the reaction vessel and the shaking mechanism behind it. All three were thus in the same straight line and the reaction vessel was shaken along this line. This method of shaking along the light beam reduces fluctuations in the light intensity during the shaking cycle.

The ultra-violet lamp used was a G.E.C. Osira high-pressure mercury arc, and it was used with the recommended choke and condenser and run at constant voltage.

Intermittent light was obtained by rotating a sheet-metal sector in front of the lamp, giving equal light and dark periods. The rate of evolution of nitrogen was measured by observing the pressure build up in the manostat. To enable the sensitivity to pressure increases to be measured, the manostat was slightly modified. Cooper and Melville's arrangement (their Fig. 2) was modified by sealing a vertical tube to the horizontal tube connecting C_2 to A_2. This vertical tube led through a capillary tap to a small bulb. Small quantities of gas could then be added to the manostat from the bulb. For the present purpose the electrolytic cell was isolated from the manostat by a tap.

The main supply of *iso*propylbenzene was kept sealed in glass. Small quantities were removed for use and stored under nitrogen in a pipette similar to that used by Cooper and Melville. Apiezon grease M was used as a general lubricant for taps and ground-glass joints, except for those in close proximity to the hydrocarbon where silicone grease was used.

Materials.—iso*Propylbenzene.* This was obtained pure for kinetic purposes. Its ultra-violet absorption spectrum was examined with a Hilger " Uvispec " Spectrophotometer. Over the range 2550—2750 Å the spectrum was identical with that of the N.B.S. standard ($99{\cdot}95 \pm 0{\cdot}02$ mole per cent. of *iso*propylbenzene). The absorption of wave-lengths transmitted by Pyrex glass, *i.e.*, greater than about 3000 Å, was negligible.

A sample of the peroxide-free *iso*propylbenzene was exposed to air for several weeks in order to allow it to accumulate peroxide. The spectrum was then measured and showed greatly increased absorption above 3000 Å. The peroxide was estimated iodometrically and so it was found that the molar decadic extinction coefficient at 3400 Å, which is near the absorption peak for azo-sensitiser, is about 0·7. It could then be calculated that the screening effect of the hydroperoxide on the sensitisers was not serious even at the maximum extent of oxidation which was obtained.

*α-Azo*iso*butyronitrile.* This was prepared according to Thiele and Heuser (*Annalen*, 1896, **290**, 1) and, recrystallised from ethanol, had m. p. 102—103° (Overberger, *J. Amer. Chem. Soc.*, 1949, **71**, 2661, gives 103—104°) with decomp. Its ultra-violet spectrum is almost identical with that reported by Overberger.

1-*Azo*-1-*cyano*cyclo*hexane.* This was obtained commercially and, recrystallised from ethanol, had m. p. 114° (Overberger gives m. p. 114°). The absorption spectrum (Fig. 1) was determined in solution (10 g./l.) in ethanol. The absorption is more intense than that of azo*iso*butyronitrile, in contrast to Overberger's finding—his values are about 60—70% of those obtained here, though the shape and the position of this spectrogram are the same as we found.

Chlorobenzene. The B.D.H. product was twice fractionated through a 1-ft. Dufton column.

Oxygen. Gas was obtained from commercial cylinders and passed through a liquid-air trap.

Nitrogen. This was of oxygen-free grade.

*Results with Azo*isobutyronitrile.—This sensitiser was found to give appreciable thermal rates if used at temperature above 50°. At 30° the thermal rate could be reduced to 10% of the total rate under irradiation, which is sufficiently low to permit investigation of the photo-reaction.

The primary product of the reaction was hydroperoxide; the yield based on the oxygen absorbed was nearly 100%. The rate dependence on light intensity was slightly less than $\frac{1}{2}$ power, and the rate was independent of oxygen pressure over the range 250—700 mm. It was subsequently found that with the amounts of catalyst used in these experiments there was an appreciable amount of nitrogen evolved in the initiation step. The true peroxide yield was therefore less than that calculated on the basis of the gas absorbed. The deviation from $\frac{1}{2}$ power dependence on the light intensity was also due to this phenomenon.

The reaction vessel was cleaned out between runs in two ways. In both cases silicone grease was removed from the cone by wiping it with cotton wool soaked in benzene. The vessel was then washed out 3 times with ethanol. It was then either pumped out to a high vacuum for 20 min., or washed 3 times with distilled water and heated in the oven, air being periodically blown through it. Both methods gave the same rates, so the first method was adopted as standard.

FIG. 1. *Ultra-violet absorption of* 1-*azo*-1-*cyano*cyclo*hexane* (ε = *molar decadic extinction coefficient*).

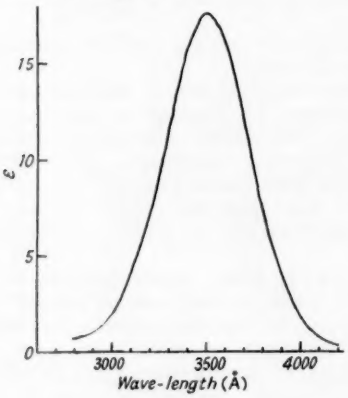
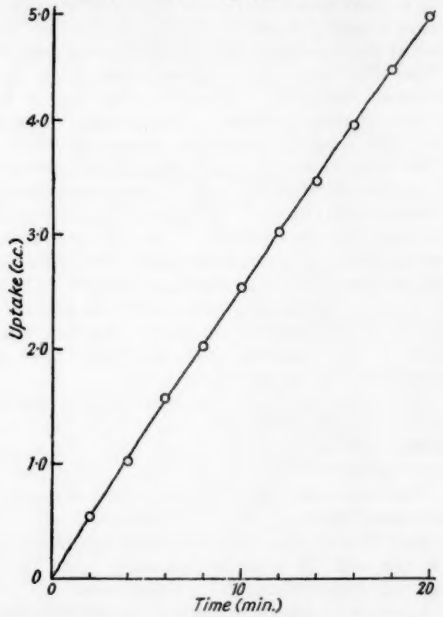


FIG. 2. *Course of reaction at* 50°.



In order to increase the kinetic chain length of the oxidation it is necessary to work at higher temperatures. For this reason the present sensitiser is unsuitable and attention was turned to a more thermally stable azo-sensitiser.

The Reaction sensitised with 1-*Azo*-1-*cyano*cyclo*hexane.*—An 0·01M-solution of the sensitiser in *iso*propylbenzene gave suitable rates of oxidation at 50°, with oxygen pressures of 175 mm. (The rate falls off with time, owing to exhaustion of the catalyst.) The course of the reaction is shown in Fig. 2, the oxidation being carried out under the standard conditions outlined later.

In all the experiments described below it was necessary on account of the short chain lengths to correct rates of oxygen absorption for the nitrogen evolved by the sensitiser when under irradiation.

Peroxide Yields.—Samples (2·2 ml.) of *iso*propylbenzene solution were oxidised at varying temperatures, and the total oxygen absorptions (in ml. at 25°/175 mm.) were measured. The hydroperoxide was estimated by an iodometric method. Iodine was liberated from potassium iodide solution in the presence of glacial acetic acid and determined by titration against 0·01N-thiosulphate. "AnalaR" reagents were used throughout and the thiosulphate was standardised against potassium iodate solutions.

Rate of Oxygen Solution.—When oxygen is being removed by reaction, the concentration of gas in solution is lowered from its saturation value. Provided that dissolution is made easy, the change in concentration is sufficiently small to be neglected.

TABLE 1. *Peroxide yield, with* 1-*azo*-1-*cyano*cyclo*hexane.*

Temp.	O_2 absorption (ml. at 25°/175 mm.)	Peroxide yield (%)	Temp.	O_2 absorption (ml. at 25°/175 mm.)	Peroxide yield (%)
30°	4·7(4)	88	58°	9·72	93
40	7·5(0)	95	65	9·86	95
50	9·24	83			Average 91

A simple way of verifying this is to observe whether there is any variation of oxidation rate with the speed of shaking of the reaction vessel. The reaction rate was measured at a high speed, at a lower shaking speed, and then again at the high speed. A typical experiment is illustrated in Fig. 3. The second rate was found to be, within experimental error, the same as the mean of the other two for rates of shaking in the range 120—300 cycles per min.; 300 cycles per min. was adopted as the standard rate of shaking. The size of sample was also kept standard at 2·2 ml. containing 5 mg. of sensitiser.

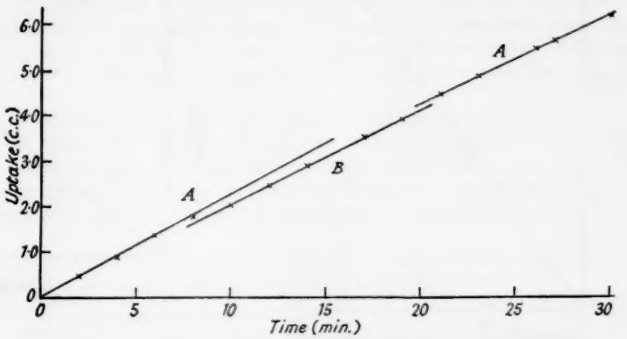


FIG. 3. *Variation of rate with speed of shaking.*
A, 300 cycles/min.
B, 130 cycles/min.

Calculation of Photo-rate.—It has been assumed that the photochemical and the thermal reaction are similar except for the initiating reaction. In these circumstances the rates of initiation are additive and the rate of oxidation due to photo-initiation (R_P) is given by

$$(R_P)^{\frac{1}{n}} = (R_L)^{\frac{1}{n}} - (R_T)^{\frac{1}{n}}$$

where R_T = thermal rate, R_L = total rate under irradiation, and n = intensity exponent later shown to be $\frac{1}{2}$. This method of obtaining the photo-rate was suggested by Noyes and Leighton ("Photochemistry of Gases," Reinhold, New York, 1941, p. 202).

Dependence of the Photo-rate on Light Intensity.—The rate was measured under a reduced light intensity and compared with the mean of the rates at full intensity measured immediately before and after the experiment. The light intensity was reduced by placing a fine calibrated wire gauze between the lamp and the thermostat. The results (Table 2) show that the exponent is $\frac{1}{2}$.

Rate Dependence on Sensitiser Concentrations.—For a photochemical reaction in which the rate is proportional to the square root of the rate of initiation, the rate will also be proportional to the square root of the sensitiser concentration providing that the light absorption is relatively

TABLE 2. *Rate dependence on light intensity.*

Temp.	Transmission of gauze	Ratio of rates R_{RP}/R_P	Intensity exponent	Rate of oxidation (10^{-5} mole $l.^{-1}$ $sec.^{-1}$)
65°	0·28	0·54	0·48	2·9
65	0·28	0·51	0·51	
50	0·28	0·51	0·53	1·75
50	0·47	0·68	0·51	
50	0·47	0·68	0·51	
50	0·47	0·69	0·49	
50	0·45	0·64	0·56	
50	0·45	0·68	0·49	
			Average 0·51	

low. The rate of oxygen absorption was measured at 50° for 2·2-ml. of *iso*propylbenzene containing varying quantities of sensitiser. The results are shown in Fig. 4.

Rate Dependence on Hydrocarbon Concentration.—Mixtures of *iso*propyl- and chloro-benzene, made up volumetrically, were oxidised under standard conditions at 50° with 5 mg. of sensitiser per 2·2-ml. sample. Fig. 5 shows a first-order dependence on hydrocarbon concentration.

Rate Dependence on Oxygen Pressure.—The variation of the rate with oxygen pressure was studied at 65° with standard samples. Fig. 6 shows that the rate is independent of oxygen pressure above about 200 mm. but below this it starts to fall off.

Overall Energy of Activation for the Photo-reaction.—A series of rate measurements at 175 mm. pressure was made over the temperature range 30—65° with a standard 2·2-ml. sample. From

FIG. 4. *Rate dependence on sensitiser concentration (at 50°).*

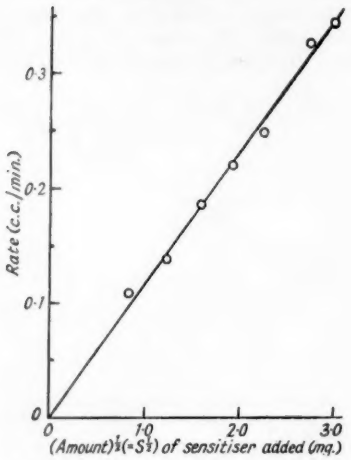
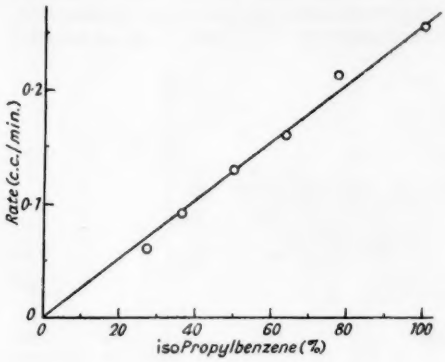


FIG. 5. *Rate dependence on hydrocarbon concentration (at 50°).*



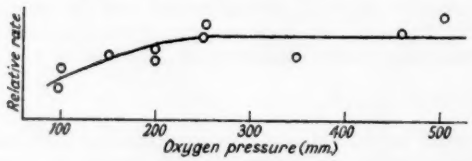


FIG. 6. *Rate dependence on oxygen pressure (at 65°).*

the plot of log rate against the reciprocal of the absolute temperature (Fig. 7) the overall energy of activation was found to be 6·53 kcal.

A second series of experiments involving many determinations at each of three temperatures was also made. The results, shown in Table 3, yield a value of 6·83 kcal.

TABLE 3.

Temp.	30°	50°	65°
Rate (10^{-5} mole $l.^{-1}$ $sec.^{-1}$)	0·881	0·175	2·88

The overall energy of activation has therefore been taken to be 6·7 kcal.

It is now possible to express the experimental results in the form of an empirical equation, giving the rate of oxidation as

$$-d[O_2]/dt = kI^{\frac{1}{2}}C^{\frac{1}{2}}[RH][O_2]^0$$

where I = light intensity, C = sensitiser concentration, and [RH] = hydrocarbon concentration. The rate of chain starting may be assumed to be proportional to the light intensity, and to the sensitiser concentration where the light is not heavily absorbed. The rate equation therefore shows a square-root dependence on the rate of initiation.

This empirical rate equation is formally analogous to those generally obtained in other

photochemical autoxidations, such as those of aldehydes and olefins, suggesting a close similarity in mechanism. With the usual nomenclature, that which has been established is

Initiation : $\mathrm{R}\cdot$ or $\mathrm{RO_2}\cdot$

Propagation : $\mathrm{R}\cdot + \mathrm{O_2} \xrightarrow{k_2} \mathrm{RO_2}\cdot$

$\mathrm{RO_2}\cdot + \mathrm{R{-}H} \xrightarrow{k_3} \mathrm{RO_2\,H} + \mathrm{R}\cdot$

Termination : $\mathrm{RO_2}\cdot + \mathrm{RO_2} \xrightarrow{k_6}$

Application of the stationary-state method for calculation of the rate of oxidation gives

$$-\mathrm{d[O_2]}/\mathrm{d}t = k_3[\mathrm{RH}]R_i^{0.5}/k_6^{0.5} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where R_i is the rate of initiation.

In deriving this expression it is assumed that the reactions of the R· radical are not rate-determining. If this were not so, the rate would become dependent on the oxygen pressure.

The exact mechanism by which azo-catalysts initiate chains in oxidation systems is not known. However, it is well established that in their thermal decomposition, nitrogen is evolved and free radicals are formed by the reaction $(\mathrm{CN{\cdot}CMe_2{\cdot}N{:}})_2 \longrightarrow \mathrm{N_2} + 2\mathrm{CN{\cdot}CMe_2}\cdot$. A similar reaction must occur under irradiation by ultra-violet light. These radicals may then undergo one of two reactions : either they abstract the tertiary hydrogen atom of the *iso*propylbenzene, or they combine with an oxygen molecule, followed by hydrogen abstraction. It has been found that many radicals react rapidly with oxygen whereas hydrogen abstraction would be expected to be slower.

It has been assumed in the present work that photolysis of the sensitiser produces two free radicals and a molecule of nitrogen. R_i, the rate of initiation, then becomes equal to twice the rate of nitrogen evolution, providing that each radical from the sensitiser starts a reaction chain. As the reaction can be initiated photochemically and the rate is proportional to the square root of the light intensity it is possible to apply the sector technique to evaluate the lifetime of the kinetic chain.

In the " high-pressure " region where the concentration of $\mathrm{RO_2}$ radicals is much greater than the concentration of R radicals, the life-time (τ) obtained is that of the former.

Now,
$$\tau = \frac{\text{Free radical concentration}}{\text{Rate of removal of free radicals}} = \frac{1}{k_6[\mathrm{RO_2}]_s} \quad . \quad . \quad . \quad . \quad (2)$$

where τ and $[\mathrm{RO_2}]_s$ refer to the values in the stationary state.

Also, in the steady state,

$$I - k_6[\mathrm{RO_2}]^2 = 0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

from (2) and (3)

$$k_6 = (\tau^2 R_i)^{-1} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

and from (1) and (4)

$$k_3 = R_L/\tau[\mathrm{RH}]R_i \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

The values of τ and R_i may thus be used in (4) and (5) to obtain the absolute velocity constants.

It is important for the present purpose that the concentration of radicals should be nearly uniformly distributed through the oxidising liquid. As the ultra-violet light was filtered through Pyrex glass, absorption by the hydrocarbon or its peroxide may be neglected.

The peak value of the molar decadic extinction coefficient for the *cyclo*hexane–azo-compound is about 17·5. The light beam traverses about 0·4 cm. of a 10^{-2}M-solution. Hence it may be shown that only about 15% of the light at the absorption peak is absorbed ; further, the shaking of the reaction vessel will help to distribute the radicals uniformly.

The square-root dependence on the sensitiser concentration also indicates the absence of a " skin effect."

Determination of the Rate of Initiation.—A standard sample was introduced into the reaction vessel, frozen in liquid air, and degassed. The system was then filled with nitrogen. When thermal equilibrium had been reached the nitrogen pressure was adjusted to a suitable value, and the taps in the manostat were closed. The pressure build-up under irradiation could be measured by following the upward rise of the silicone fluid B_2.

At lower temperatures it was possible to take readings during the time of irradiation, plot the results graphically, and draw a smooth curve. At higher temperatures the mean position of the level before and after irradiation was measured. The rate of nitrogen evolution in the latter case is therefore less accurately known, but should be within $\pm 10\%$.

The manostat was filled with pure nitrogen to a suitable high pressure (P), and the capillary tap turned to isolate the bulb. The apparatus was then adjusted to pressure (p), as previously described, for measurement of the nitrogen evolution. The silicone level was noted. Finally, the capillary tap was opened and the resulting movement of the silicone was noted. The volume of gas (V_1) isolated at the higher pressure is equal to the volume of the bulb and of the capillary through the tap key. The latter was estimated, by filling with mercury and weighing, to be 0·49 ml.

If the nitrogen in the bulb was at a pressure P and if the final pressure in the manostat was p', then the amount of gas added to the manostat is V_1 ml. at $(P - p')$ mm. and room temperature.

As the volume V_1 is small, the error in assuming $p' = p$ should be small. By connecting the manostat to a manometer it was verified that this was so.

FIG. 7. *Energy of activation of photo-oxidation.*

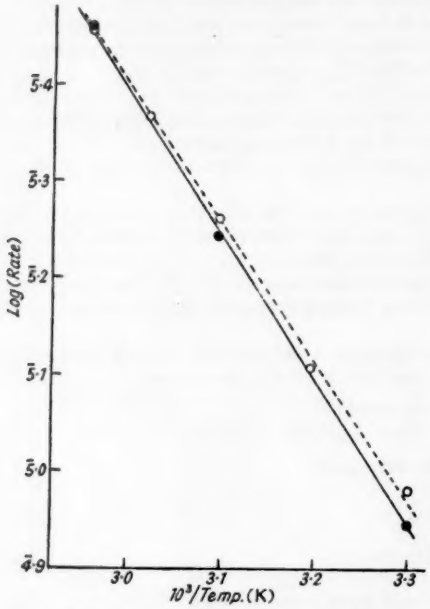
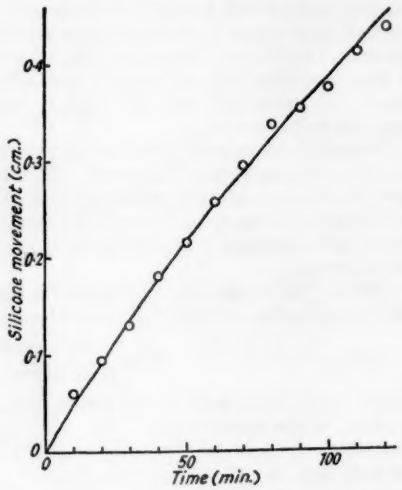


FIG. 8. *Nitrogen evolution at* 350 *mm.*



Full points refer to values on p. 948.

A second method used to check the sensitivity of the manostat was to alter the temperature of the bulb of the reaction vessel. If its volume is V, then it can be shown that for an apparatus of the dimensions used, $\Delta T/T = \Delta V/V$, where T is the original temperature, ΔT = the change in temperature, and ΔV = the gas evolved which produces the same response by the manometer.

There was no measurable delay between irradiation and gas evolution, and the evolution ceased when the lamp was switched off.

A typical experimental run is shown in Fig. 8. The rate fell off considerably during measurement (120 min.) owing to exhaustion of the sensitiser. The results during the first 10 min. are shown in Table 4. For 1-cm. movement of the silicone oil, $P - p = 909$ mm., and therefore movement of 1 cm. = 0·49 ml. of gas at 20°/909 mm. = $2{\cdot}47 \times 10^{-5}$ mole, and therefore the rate of nitrogen evolution = $11{\cdot}9 \times 10^{-8}$ mole per min.

The bulb of the vessel has a volume of 15·6 ml. and a temperature change from 49·95° to 43·3° alters the silicone level by 0·365 cm. Use of equation (6) shows that a 1-cm. movement of the silicone = $2{\cdot}2 \times 10^{-5}$ mole. The agreement is satisfactory as equation (6) is only approximately correct.

Further results are shown in Table 5.

TABLE 4. *Nitrogen evolution at* 50°/350 *mm.*

Expt.	Rate of movement of silicone level (10^{-3} cm./min.)	Pressure (mm.) in bulb (P)	Pressure (mm.) in manostat (p)	Silicone oil movement S	$10^3S/(P-p)$
1	4·2	—	—	—	—
2	5·3	705	351	0·382	1·08
3	5·3	705	351	0·400	1·13
4	5·4	715	350	0·395	1·08
5	5·2				Mean 1·1
6	3·8				
7	4·6				
	Mean 4·8				

TABLE 5. *Nitrogen evolution at* 50°/100 *mm.* [*pressure* (p) *in manostat* = 100 *mm.*].

Rate of movement of silicone level (10^{-3} cm./min.)	1·15	1·32	1·40
Pressure (P) in bulb (mm.)	228	227	227
Silicone movement (S) (cm.)	0·360	0·360	0·367

Hence $S/(P-p) = 2{\cdot}85 \times 10^{-3}$, and the rate of nitrogen evolution = $11{\cdot}9 \times 10^{-8}$ mole/min.

TABLE 6. *Nitrogen evolution at* 30°/100 *mm.* (*pressnre in bulb* 230 *mm.*; *pressure in manostat* 100 *mm.*)

Rate of movement of silicone level (cm./min.)	1·14	1·13	1·13	1·15	1·15	1·15	—	—
Silicone movement (cm.).....	0·357	0·380	0·360	0·378	0·373	0·358	0·356	0·361

The rate of nitrogen evolution = $10{\cdot}8 \times 10^{-8}$ mole/min.

TABLE 7. *Nitrogen evolution at* 65°/100 *mm.*

Rate of movement (10^{-2} cm./min.) (4 expts.): 1·44, 1·15, 1·21, 1·22 (mean 1·25).
Sensitivity: $9{\cdot}08 \times 10^{-6}$ mole per cm. movement.
Rate of nitrogen evolution = $11{\cdot}45 \times 10^{-8}$ mole/min.

TABLE 8. *Collected values for rate of nitrogen evolution.*

Temp.	Pressure (mm.)	No. of determinations	Rate (10^{-8} mole/min.)
30°	100	6	10·8
50	100	3	11·9
65	100	4	11·4
50	350	7	11·9
			Mean 11·3

A weighted mean was used; as the results at 30° were the most reproducible these were multiplied by 2.

From the rate of evolution the rate of initiation was found to be $1{\cdot}72 \times 10^{-6}$ mole l.$^{-1}$ sec.$^{-1}$.

At 50°, the rate of oxidation = $1{\cdot}75 \times 10^{-5}$ mole l.$^{-1}$ sec.$^{-1}$; hence the kinetic chain length is 10 and $k_3k_6^{-\frac{1}{2}} = 3{\cdot}04 \times 10^{-3}$ mole$^{-\frac{1}{2}}$ l.$^{\frac{1}{2}}$ sec.$^{-\frac{1}{2}}$.

At 65°, the rate of oxidation = $2{\cdot}88 \times 10^{-5}$ mole l.$^{-1}$ sec.$^{-1}$, and the chain length is 17; $k_3k_6^{-\frac{1}{2}} = 3{\cdot}04 \times 10^{3}$ mole$^{-\frac{1}{2}}$ l.$^{\frac{1}{2}}$ sec.$^{-\frac{1}{2}}$.

It is of interest to compare the value of the rate of initiation as determined directly with the value obtained by using the data for the thermal decomposition.

The oxidation rate at constant temperature is proportional to the square root of the rate of initiation. Hence $I_P = I_TR_P^2/R_T^2$, where I_P and I_T are the photo- and the thermal rates of initiation, the latter being equal to twice the rate of sensitiser decomposition; and R_P and R_T are the oxidation rates. Lewis and Matheson (*J. Amer. Chem. Soc.*, 1949, **71**, 747) state that, for 1-azo-1-cyano*cyclo*hexane, k for the first-order decomposition at 80° is $2{\cdot}82 \times 10^{-4}$ min.$^{-1}$, and the energy of activation is 39·9 kcal. per mole. Overberger, O'Shaughnessy, and Shalit (*ibid.*, p. 2661) report that at 80·2° $k = 0{\cdot}083$ sec.$^{-1}$ = $4{\cdot}98 \times 10^{-4}$ min.$^{-1}$. Arnett (*ibid.*, 1952, **74**, 2027) gives $k = 3{\cdot}2 \times 10^{-4}$ min.$^{-1}$ at 77°, or, using Matheson's energy of activation, $k = 5{\cdot}2 \times 10^{-4}$ min.$^{-1}$ at 80°.

The thermal rate at 80° was measured and compared with the " light " rate obtained with a filter of transmission = 0·28, with the following results:

Thermal rate	0·0570	0·0655	0·059	
" Light " rate	0·1145	0·1080	0·1190	
Rate of initiation (10^{-8} mole/min.)	12·9	7·1	13·2	(mean 11·1)

These values have been obtained by using Matheson's data. The directly determined value is about twice as great ($22{\cdot}6 \times 10^{-8}$). Using the results of Overberger or of Arnett gives a value 20×10^{-8} which is in good agreement with the determined value.

It will be noted from Table 8 that there does not appear to be any effect due to temperature on the photo-rate of sensitiser decomposition. This is as might be expected for a photolytic process not complicated by a secondary reaction.

Determination of the Life-time.—The use of intermittent illumination for the determination of free-radical life-times is well established, and, for a similar system, the general procedure has already been described (Cooper and Melville, *loc cit.*) and has been used in both polymerisation and autoxidation studies (Bateman and Gee, *Proc. Roy. Soc.*, 1948, A, **195**, 376).

FIG. 9. *Life-time at* 50°.

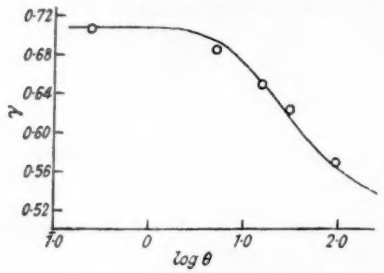
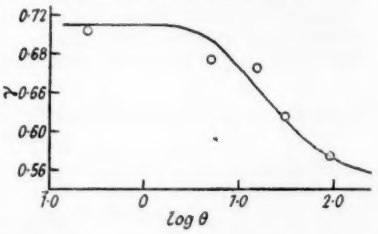


FIG. 10. *Life-time at* 65°.



The experimental procedure in the measurement of the life-time is similar to that described previously for measuring the intensity exponent. Measurements were made of the initial thermal rate during about 20 min. and of the light rate during about 8—10 min. The sector was started, and after about 1 min., during which the system becomes steady, the rate in intermittent light was measured. The sector was timed with an ordinary stop-watch and the rate measurement continued for about 10 min. The uninterrupted rate was again measured, and finally the thermal rate.

Several determinations were made at each flash time and the averaged results are shown in the following Tables, where Y = ratio of rate in intermittent light to that in uninterrupted light, and α = ratio of thermal to " light " rate.

Determination of τ *at* 50° ; $\alpha = 0{\cdot}04$.

Flash time (θ) (sec.)	0·243	5·0	15·0	30·0	90·0
Y	0·7060	0·6846	0·6496	0·6226	0·5678

Determination of τ *at* 65° ; $\alpha = 0{\cdot}10$.

Flash time (θ) (sec.)	0·248	5·0	15·0	30·0	90·0
Y	0·7038	0·6730	0·6649	0·6141	0·5729

The usual plot of γ against log θ is shown in Figs. 9 and 10 with the life-time curve in the position of best fit. This gives $\tau = 4{\cdot}6$ sec. at 50°, and 4·2 sec. at 65°. The difference, which is within expermental error, would correspond to an energy of activation for termination of about 0·25 kcal. However the precision of the data is only sufficient to establish that its value is less than 6 kcal.

Collected Kinetic Data.

	At 50°	At 65°
Rate of oxidation (mole l.$^{-1}$ sec.$^{-1}$)	$1{\cdot}75 \times 10^{-5}$	$2{\cdot}88 \times 10^{-5}$
Rate of initiation (mole l.$^{-1}$ sec.$^{-1}$)	$1{\cdot}72 \times 10^{-6}$	$1{\cdot}72 \times 10^{-6}$
Life-time of reaction chain (sec.)	4·6	4·2
k_3 (mole^{-1} l. sec.$^{-1}$)	0·31	0·56
k_6 (mole^{-1} l. sec.$^{-1}$)	$2{\cdot}8 \times 10^4$	$3{\cdot}3 \times 10^4$
$E_3 - \frac{1}{2}E_6$ (kcal./mole)	6·7	

The authors are much indebted to the Distillers Company Limited for gifts of specially purified *iso*propylbenzene. One of them (S. R.) is indebted to the Department of Scientific and Industrial Research for a maintenance allowance.

CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15.

[*Received, September 24th,* 1953.]

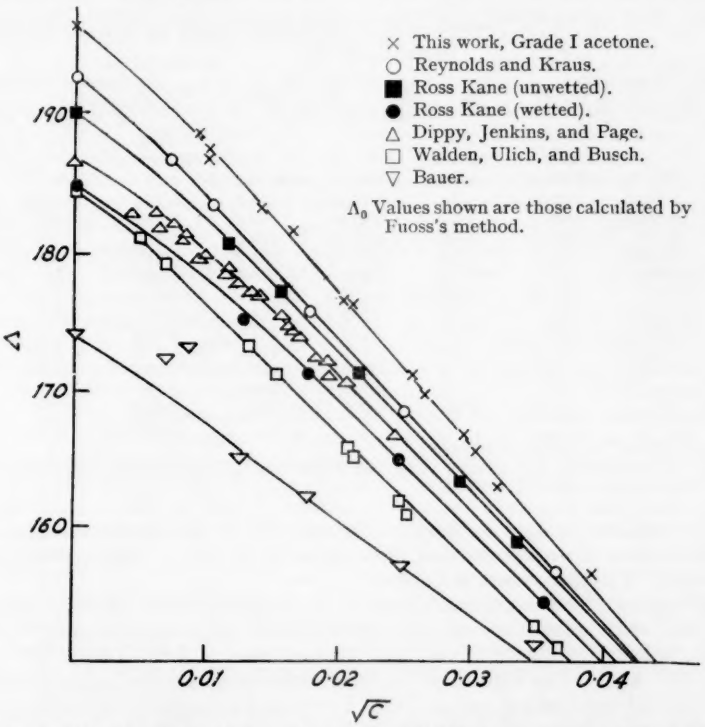
Conductimetric Studies in Ketonic Solvents. Part I. Acetone as Solvent.

By J. F. J. Dippy and S. R. C. Hughes.

[Reprint Order No. 4791.]

The literature reveals instances of serious lack of agreement in conductivity data for uni-univalent salts in acetone and these may be largely attributable to the variable water content of the specimens of solvent; this view is elaborated by an examination of the data relating to potassium iodide solutions. For some data Bjerrum's and Stokes's equations have been combined to allow estimates of the ionic radii of the solute to be made. It appears that, although a moderate total solvent correction is permissible, yet for valid conclusions to be reached from a comparison of conductivity data for acetone solutions, large divergence in solvent quality must be avoided.

Between 1926 and 1948 no less than six papers [Walden, Ulich, and Busch, *Z. physikal. Chem.*, 1926, **123**, 429; Bauer, *Ann. Physik*, 1930, **6**, 253; Hartley and Hughes (Ross Kane), *Phil. Mag.*, 1933, **15**, 610; Blokker, *Rec. Trav. chim.*, 1935, **54**, 975; Dippy, Jenkins, and Page, *J.*, 1939, 1386; Reynolds and Kraus, *J. Amer. Chem. Soc.*, 1948, **70**, 1709] have



recorded the equivalent conductivity of potassium iodide in acetone at 25° as a function of concentration (see Fig.). The highest conductivities are due to Reynolds and Kraus, who claimed that their materials were of superior quality, in particular the solvent, for which new physical data were advanced. These authors deplore the use of a non-aqueous solvent of such a quality as to require a solvent correction; as their acetone had a specific conductance of $1—2 \times 10^{-9}$ mho they seemed entitled to make this criticism, although all previous work (*loc. cit.*) had employed moderate total solvent corrections, for acetone whose conductance

varied between 10^{-7} and 10^{-8} mho, with some apparent success. A further examination of this question has now been undertaken with special reference to potassium iodide (a solute common to the data of most workers) in acetone of different qualities, referred to as Grades I, II, and III.

Grade I acetone was prepared in an attempt to reproduce Reynolds and Kraus's data (*loc. cit.*), although their purification procedure (*viz.*, agitation with anhydrous calcium chloride followed by two distillations from activated alumina) was modified so as to use the alumina more effectively and to safeguard the product from atmospheric contamination. Nevertheless, our lowest specific conductance was 8×10^{-9} mho, and in no case after standing at 25° was a value less than $1{\cdot}5 \times 10^{-8}$ mho recorded. As, however, consistent values of Λ_{KI} were found with independent batches of solvent whose specific conductances ranged from $2{\cdot}09 \times 10^{-8}$ to $2{\cdot}36 \times 10^{-8}$ mho, it is considered that there is no serious objection to a moderate total solvent correction.

It is difficult to see why solvent and solute conductance should not be additive unless the former could be traced to some weak electrolyte showing an altogether phenomenal salt effect in the solvent of low dielectric constant. Furthermore, the uncorrected Λ values of most other authors remain below those of Reynolds and Kraus by amounts totally inexplicable on such a basis. The equivalent conductivities measured by us for potassium iodide in Grade I acetone (right-hand columns, Table 1) are, on the other hand,

TABLE 1. *The equivalent conductivities of potassium iodide in acetone of different qualities at 25°.*

Grade III acetone By Fuoss plot : $\Lambda_0 = 181{\cdot}8$; $K = 24{\cdot}2 \times 10^{-3}$			Grade II acetone By Fuoss plot : $\Lambda_0 = 188{\cdot}7$; $K = 12{\cdot}96 \times 10^{-3}$			Grade I acetone By Fuoss plot : $\Lambda_0 = 196{\cdot}6$; $K = 9{\cdot}13 \times 10^{-3}$		
$10^7\kappa$ (Solvent), mho	10^4C *	Λ corr.	$10^7\kappa$ (Solvent), mho	10^4C *	Λ corr.	$10^7\kappa$ (Solvent), mho	10^4C *	Λ corr.
1·6	0·1812	180·2	1·34	0·2909	184·7	0·236	0·8704	188·8
1·6	0·3040	180·1	1·34	0·6220	182·5	0·209	1·007	186·9
3·4	2·747	169·9	1·69	0·6348	183·8	0·213	1·055	187·7
2·9	3·863	166·6	1·34	0·8742	181·3	0·210	1·953	183·3
2·9	8·381	158·7	0·88	1·221	179·1	0·236	2·675	181·7
3·0	11·79	155·3	1·34	1·336	179·8	0·210	4·124	176·6
3·0	18·78	148·1	0·88	1·380	178·7	0·236	4·317	176·4
3·0	30·87 †	143·2	1·65	1·618	177·9	0·236	6·495	171·1
3·4	38·95 †	135·9	1·34	1·778	178·5	0·210	6·950	169·8
2·9	83·92 †	115·9	0·88	2·970	175·0	0·236	8·555	166·8
			0·88	5·321	169·4	0·210	9·189	165·6
			0·88	8·206	163·7	0·236	10·186	162·9
						0·236	15·370	156·7

* Concentrations, C, are in mole litre^{-1}.

† These concentrations are greater than the Fuoss critical concentration for acetone and are omitted in the calculation of Λ_0 and K.

higher than those of any other workers. Determination of the densities of three samples of this acetone gave the smallest value hitherto recorded, *viz.*, 0·7840 ± 0·0001 (vacuum corrected) at 25° (cf. other values in Table 2).

Solvents having higher specific conductivities (Grades II and III) were obtained by drying acetone with anhydrous calcium chloride and anhydrous potassium carbonate, respectively, before fractionation, and had conductances of $0{\cdot}88$—$1{\cdot}69 \times 10^{-7}$ mho and $1{\cdot}6$—$3{\cdot}4 \times 10^{-7}$ mho. The equivalent conductivities of potassium iodide in solvents of Grades II and III are also set out in Table 1; those for Grade II resemble the data of Dippy, Jenkins, and Page, and those for Grade II the data of Walden, Ulich, and Busch. It is significant that within these moderate ranges of varying solvent conductance a total solvent correction gives self-consistent results for each grade.

EXPERIMENTAL

Measurement of Conductivity.—In essentials, the bridge network was based on the Jones and Josephs bridge (*J. Amer. Chem. Soc.*, 1928, **50**, 1067). The current was applied to the bridge from the push-pull outputs of the distant oscillator by means of two 5000-ohm potentiometers

in series, with their junction earthed. The ratio arms of the bridge consisted of two 1000-ohm non-inductively wound resistances. The variable resistance arm consisted of two high-quality calibrated, low-inductance resistance boxes, one a single decade box of total resistance 1,000,000 ohms which was shorted out when not required, and the other a six-decade box having a total resistance of 111,111 ohms, adjustable to 0·1 ohm; two six-decade boxes were available for comparison. Variable capacitances of from 0·000025 μF to 0·02 μF could be applied across the resistance boxes or the conductivity cell, and also between earth and either end of the bridge, in each case by means of a variable 0·0005 μF air condenser and two banks of fixed mica condensers on decade switches. The method of obtaining balance was the same as described by Jones and Josephs.

The oscillator consisted essentially of two valves forming a resistance-capacity oscillator in which the frequency was determined by a Wien bridge network, the controlling element being a thermistor. Provision was made for coarse frequency control by means of switched condensers and for fine frequency control by means of a ganged wire-wound potentiometer. The output was fed into a pair of anode-follower valves, arranged to give a push-pull output. The high value of negative feedback in the output stages and the control exerted by the thermistor resulted in a highly stable, pure sine-wave and an extremely low hum level. The oscillator was set at 1000 cycles per sec. throughout this work.

The amplifier consisted of three pentodes, across the second of which could be switched a parallel T-filter. Negative feedback was then applied to the second valve at all frequencies other than that to which the filter was tuned. The output of the third pentode was fed to the grids of a double triode which gave an output on the headphones and on a cathode-ray tuning indicator. A signal of 0·1 microvolt could be detected in the headphones.

The cell employed in connection with acetone of Grades II and III was similar to that described by Dippy, Jenkins, and Page (*loc. cit.*), whereas a cell of the Erlenmeyer type, similar to that described by Reynolds and Kraus, having greyed platinum electrodes 1 cm. apart, was used for Grade I acetone. The cell constants were measured by the intermediate cell method, using a directly calibrated cell (constant 0·25926) also with greyed electrodes. Calibration with intermediate potassium chloride solutions of concentrations from M/500 to M/50,000 showed a constant ratio of cell constants as did series-parallel measurements with the two cells. The basic cell-constant was determined by using " AnalaR " potassium chloride (twice recrystallized from conductivity water and fused in a platinum dish) weighed on a microbalance and dissolved in " equilibrium " conductivity water of $\kappa = 0{\cdot}8 \times 10^{-6}$ mho. Jones and Prendergast's conductance data (*J. Amer. Chem. Soc.*, 1937, **59**, 731) were employed.

Materials and Solvent.—All acetone was initially of " AnalaR " quality, the dates of purchase being Grade III, 1947–48; Grade II, 1949–51; Grade I, 1951–53. The quality of these products as judged by distillation behaviour and conductivity, improved steadily over this period. After the drying treatment appropriate to the particular grade, acetone was fractionated in an all-glass still having a 20" column packed with glass rings. Distillation was finely controlled by means of a regulated Thermomantle heater. Anhydrous potassium carbonate and calcium chloride, of reagent standard, were oven-dried at 140° before use. The alumina used for preparation of Grade I solvent was Spence's Type A (Harshaw's AL 4, as used by Reynolds and Kraus, was found to have no different effect). " AnalaR " potassium iodide was recrystallized twice from conductivity water, dried at 120°, and stored in a vacuum-desiccator.

In the preparation of Grade I acetone, Reynolds and Kraus's procedure (*loc. cit.*) was modified. " AnalaR " acetone, after being shaken over calcium chloride for 4 days, was filtered rapidly into a Pyrex flask containing fresh, cold alumina which had been baked out at 120°. After its contents had gently refluxed for 2—3 hr., the flask was closed whilst hot, and left in the dark for 7—10 days, after which, rapid filtration on to fresh alumina, refluxing, and standing were repeated. Before final fractionation, the acetone was filtered rapidly into the distillation flask previously baked out.

The receiving end of the still was encased in a " dry-space " consisting of a 12" cubical Perspex box, constructed in part by Visijar Ltd. (Croydon), closed by a triple-beaded lid at one side to give an air-tight fit. The adaptor of the still, drilled above the nozzle to avoid spraying, was luted into the roof of this box. Manipulation within the dry-space was performed through surgical gloves let into one side, and renewed at regular intervals. A current of dry air was circulated in the box so as to maintain a continuous positive pressure. Distillation receivers, including the conductivity cell, and weighed stoppered tubes of solute were arranged on a tray resting on the floor of the box, which could be rotated to bring the objects into reach.

Conductivity Procedure.—Work in acetone of Grades II and III followed precisely the tech-

nique of Dippy, Jenkins, and Page (*loc. cit.*) but specialized procedure was needed in the case of Grade I acetone by reason of its extreme sensitivity to contamination. The cell was washed with distilled acetone, drained, and then conditioned in the dry-space for 30—40 min. before being capped. After being weighed, it was returned to the dry-space for 20—30 min. before receiving the appropriate middle fractions from the still (this was normally some 350 g. of acetone collected from two distillations). It was re-capped, left for *ca.* 30 min., and withdrawn for re-weighing, and the solvent conductivity then measured at 25° over a period of 1 hr.; a calibrated megohm shunt was used for the highest solvent resistance measurements. The cell (after its outside wall had been washed with distilled acetone) was returned to the dry-space together with sealed, weighed micro-tubes containing finely powdered potassium iodide. After 30 min. the cell was uncapped, and the contents of one or more of the micro-tubes added to it. The cell (re-capped) was placed in the thermostat (controlled within 0·005° by adjustment of the threshold heating) and the micro-tubes were re-weighed on a microbalance. The salt had dissolved after 1 hr. and the conductivity of the solution was then followed for a further hour.

The bottle used in the density determinations was manipulated within the dry-space (for Grade I acetone) and calibration was effected with conductivity water at 25°. All weighings were vacuum-corrected.

Karl Fischer Titrations.—The modified Karl Fischer reagent, for use with ketones, as specified by Mitchell and Smith (" Aquametry," Interscience Publ., 1948), was used in a burette protected from moisture. Titrations took place in a 175-c.c. conical flask fitted with an electromagnetic stirrer and sealed-in platinum electrodes which indicated the end-point potentiometrically by iodide depolarization; the flask was supplied with dry air during the titration. Calibration of the reagent was effected by means of Grade I acetone to which weight additions of conductivity water were made.

Discussion

Owing to considerable association of salts in solvents of low dielectric constant, Onsager's expression takes the form

$$\Lambda = \alpha(\Lambda_0 - S_\Lambda\sqrt{\alpha C})$$

to which conductivity data may be fitted by Fuoss's procedure (*J. Amer. Chem. Soc.*, 1935, **57**, 489) to give consistent values of Λ_0 and the coulombic dissociation constant K. The equation provides for curvature of the Λ–$\sqrt{C}$ function in the low concentration region, although, with the exception of Hughes and Hartley (*loc. cit.*) and of Dippy, Jenkins, and Page (*loc. cit.*), few authors have noted this region and only in the latter case has extrapolation to Λ_0 been obtained through it. Before 1948 all data for the conductivity of potassium iodide in acetone were presented in the traditional Kohlrausch manner, and Λ_0 values obtained by simple linear extrapolation. With the exception of Dippy, Jenkins, and Page, all such authors obtained Λ_0 values which were some 1% high.

In order to compare the data of previous authors with those of Reynolds and Kraus, and with those reported here, it has been necessary to recalculate them after Fuoss's method. The outcome of this analysis is summarized in Table 2, which also includes

Table 2.

Authors	d_4^{25}	$10^3\eta_0^{25}$	Λ_0 (Fuoss)	Λ_0 (Kohlrausch)	10^3K
This work (Grade I)	0·7840	—	196·6	199·0	9·13
Reynolds and Kraus [1]	0·7845	3·040	192·8	194·5	8·02
Ross Kane (" unwetted " solvent) [2]	0·7850	3·075	190·1	192·1	11·93
Dippy, Jenkins, and Page [3]	—	—	186·8	186·0	18·6
Ross Kane (" wetted " solvent) [2]	0·7874	3·14	185·0	187·1	16·3
Walden, Ulich, and Busch	0·7862	3·158	184·4	185·6	9·30
Bauer [4]	0·79	—	173·9	176·0	29·7

[1] These workers analyzed their data by Fuoss's method, although it is interesting that their six points lie on a straight line both in this and in the Kohlrausch plot. The solvent correction could be neglected. [2] Data, without details, released by Hartley and Hughes (*loc. cit.*). A solvent correction of $1{\cdot}8 \times 10^{-8}$ mho is employed throughout for the " unwetted " acetone. In this analysis, a dielectric constant of 20·88 was taken for the " wetted " acetone (0·769% added water). [3] These authors, employing somewhat variable solvent corrections, publish 26 points, a feature absent from earlier work. The comparison between the Fuoss and Kohlrausch values of Λ_0 shows the extent to which the low-concentration data are consistent. [4] This author's data are scanty and scattered. The density figure is mentioned in connection with a mathematical discussion and may not be experimental although it agrees markedly with his value for Λ_0.

density and viscosity data. Blokker's results (*loc. cit.*) have no place in this table as only one point (at 25°) is below the Fuoss critical concentration for acetone. This, however, lies very close to those obtained here for Grade I acetone and, had our density been employed, would have shown even greater agreement. It is noteworthy that Blokker's solvent was free from traces of methanol, and was intensively dried over calcium chloride before fractionation.

The data of Table 2, coupled with those derived from Table 1, reveal a trend which strongly suggests that the variable factor in these solvent grades is the water content. The effect of water on acetone solutions of potassium iodide has already been shown (Hughes and Hartley, *loc. cit.*) to be a preferential solvation of the potassium ion, increasing its effective radius. Such a factor, apart from reducing the value of Λ_0, should enhance the degree of dissociation of the salt in a medium of given dielectric constant, by reason of the reduced surface field of the cation. Examination of Table 2 shows this to be broadly the case.

Separate Stokes radii for the potassium and iodide ions may be derived in the cases of Reynolds and Kraus (who determined ion conductances by the method of Fowler and Kraus (*J. Amer. Chem. Soc.*, **1940**, **62**, 2237) and of Walden, Ulich, and Busch, to whose measurements, presumably, the ion conductances of Ulich and Birr (*Z. angew. Chem.*, 1928, **41**, 443) relate. The sum of these is compared in Table 3 with the total ionic radii calculated from Bjerrum's expression (*Kgl. Danske Videnskab. Selsk.*, 1926, **7**, No. 9) for coulombic dissociation in dielectric media :

$$\log Q\,(b) = 3 \log D - (\log K + 6{\cdot}120)$$

and

$$\log (r_+ + r_-) = -(\log b + \log D + 5{\cdot}254)$$

TABLE 3.

	Stokes radii (Å)			Bjerrum sum (Å)
	r_{K^+}	r_{I^-}	$r_{K^+} + r_{I^-}$	$r_{K^+} + r_{I^-}$
Walden, Ulich, and Busch	3·67	2·23	5·90	5·70
Reynolds and Kraus	3·33	2·39	5·72	5·19

This comparison shows that there is no great incompatibility between radii given by Stokes's law and those obtained from Bjerrum's theory. On combining $\Sigma(1/r_i)$ (Stokes) with Σr_i (Bjerrum) a quadratic in r_i is obtained which, provided $(\Sigma r_i)^2 > 4\Sigma r_i/\Sigma(1/r_i)$, may be solved to give two unequal roots identifiable severally with r_{K^+} and r_{I^-}. The results of this analysis are shown in Table 4. In the case of Reynolds and Kraus, the roots are unreal, so their Stokes radii are given instead, in parentheses.

TABLE 4

	$10^{-8}\Sigma(1/r_i)$, cm.$^{-1}$ (Stokes)	$10^8\Sigma r_i$, cm. (Bjerrum)	r_{K^+}, Å	r_{I^-}, Å
This work, Grade I	0·7336	5·63	3·27	2·36
Reynolds and Kraus	0·7194	5·19	(3·33)	(2·39)
Ross Kane, " unwetted "	0·7174	6·79	4·84	1·96
This work, Grade II	0·7136	7·17	5·26	1·91
Dippy, Jenkins, and Page	0·7063	8·79	7·02	1·77
Ross Kane, " wetted "	0·7131	8·24	6·44	1·79
Walden, Ulich, and Busch	0·7153	5·70	3·48	2·22
This work, Grade III	0·7052	9·78	8·06	1·72
Bauer	0·6745	10·45	8·66	1·79

The iodide radius may be taken as relatively independent of solvent quality, whereas that of the potassium ion is more than doubled over the whole range of reported data. No special criticism of Reynolds and Kraus is implied by the failure of their data to conform to this analysis.

In order still further to test the view that variable water content has hitherto been the cause of discrepancies between conductivity data in acetone, the water impurity in our solvents was estimated by the modified Karl Fischer technique (see Experimental). This analysis was performed on samples of bulked Grade I acetone of known density, portions

of which were used for a control experiment in which the equivalent conductivity of potassium iodide at 10^{-4} M-concentration was determined. Similar analyses were conducted upon two further specimens of bulked Grade I acetone (referred to as I*a*) to which additions of water had been made by weight. The following table relates water content to the other relevant data.

Source	Total wt. % of H_2O based on K. Fischer anlysis	d_4^{25}	Λ_{KI} at $c = 10^{-4}$
Grade I	0·18	0·7840	188·0
,, I*a*	0·22	0·7841	187·5
Reynolds and Kraus	—	0·7845	184·0
Ross Kane, " unwetted "	—	0·7850	182·2
I*a* + 0·65% of added H_2O	0·87	0·7861	184·0
Ross Kane, " wetted "	—	0·7874	178·0
I*a* + 1·43% of added H_2O	1·65	0·7882	178·5
Bauer	—	0·79	168·2

It may be concluded, therefore, that conductivity data for acetone solutions, in order to have comparative value, need not necessarily relate to the anhydrous medium (if that is attainable) but to comparable conditions of solvation of the ions concerned. In this connection it should be appreciated that traces of water will have a more profound influence upon ionic mobility than similar traces of electrolyte impurity.

The authors' grateful thanks are offered to Dr. D. J. G. Ives for valuable advice given at an early stage of this work, and to Mr. P. J. Black for the design and construction of the oscillator and amplifier.

CHEMISTRY DEPARTMENT,
CHELSEA POLYTECHNIC, LONDON S.W.3. [*Received, November* 13*th*, 1953]

Steroids. Part VII. Some 5-Hydroxy-derivatives of Cholestane.*

By A. J. FUDGE, C. W. SHOPPEE, and G. H. R. SUMMERS.

[Reprint Order No. 4803.]

The course of ionic dehydration of some 5α-hydroxy-steroids has been examined; a new route to *epi*cholesteryl chloride has been discovered, and the 6-epimeric cholestane-3α : 5 : 6-triols have been prepared. The mildest conditions for oxidation of 3β : 5α-dihydroxy-steroids to 5α-hydroxy-3-oxo-steroids and for dehydration of the latter to Δ^4-3-oxo-steroids have been investigated. 5-Acetoxycholestan-3β-ol resists oxidation with chromium trioxide in acetic acid at 20°; this resistance appears to arise from steric hindrance at $C_{(3)}$ by the 5α-acetoxy-group and may be a general property of 5α-acyloxy-steroids.

THE ready ionic dehydration of 6β-hydroxy-steroids of the cholestane series [5α-H(polar)/6β-OH(polar); *trans*], which appears to be independent of configuration at $C_{(3)}$, has been used previously for the preparation of the cholesteryl and *epi*cholesteryl halides (Shoppee and Summers, *J.*, 1952, 1786, 1790). It appeared of interest to examine the inverse case of the ionic dehydration of 5-hydroxy-steroids of the cholestane series [5α-OH(polar)/4β- or 6β-H(polar); *trans*] and the dependence or otherwise of its course on the presence and configuration of a substituent at $C_{(3)}$.

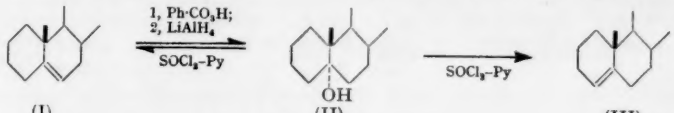
Cholestan-5-ol (II), prepared from cholest-5-ene (I) by conversion into the 5 : 6α-epoxide (Ruzicka, Furter, and Thomann, *Helv. Chim. Acta*, 1933, **26**, 333) and reduction of this with lithium aluminium hydride (cf. Plattner, Petrzilka and Lang, *ibid.*, 1944, **27**, 513), by dehydration with thionyl chloride–pyridine gave a mixture of cholest-5- (I) and -4-ene (III) in approximately equal proportions.† This behaviour may be compared with that of 5-chlorocholestane (cf. Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 1066, footnote 28) which by dehydrochlorination with ethanolic potassium acetate gives chiefly cholest-4-ene,

* Part VI, *J.*, 1953, 3683.

† The production, by pinacolic rearrangement, of 5β-methyl-19-norcoprost-9-ene is not excluded.

probably accompanied by some cholest-5-ene (cf. Mauthner, *Monatsh.*, 1907, **28**, 1113; Wettstein, Miescher, *et al.*, *Helv. Chim. Acta*, 1946, **29**, 627, especially 629).

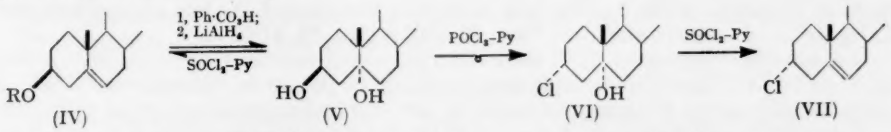
Cholestane-3β : 5-diol (V), prepared from cholesterol (IV; R = H) by reduction of the 5 : 6α-epoxide with lithium aluminium hydride (Plattner, Heusser, and Feurer, *Helv. Chim. Acta*, 1949, **32**, 587; cf. Plattner, Petrzilka, and Lang, *loc. cit.*), by treatment as the 3-monoacetate with thionyl chloride–pyridine gave cholesteryl acetate (IV; R = Ac) which appeared to be unaccompanied by 3β-acetoxycholest-4-ene. This result may be compared with the dehydrochlorination with potassium acetate of 5-chlorocholestan-3β-ol [≡ cholesterol hydrochloride] to a mixture of cholesterol and cholest-4-en-3β-ol (Windaus, *Annalen*,



(I) (II) (III)

(Py = pyridine.)

1927, **453**, 101; Schoenheimer and Evans, *J. Biol. Chem.*, 1936, **114**, 567), and with the dehydrochlorination with dimethylaniline of 3β-acetoxy-5-chlorochola-20(22) : 23-diene and its 22-bromo-derivative to mixtures of chola-4 : 20(22) : 23- and -5 : 20(22) : 23-triene in which the latter predominated (Wettstein, Miescher, *et al.*, *loc. cit.*). When the diol (V) was treated with thionyl chloride–pyridine cholesteryl sulphite was produced, but use of phosphorus oxychloride–pyridine gave 3α-chlorocholestan-5-ol (VI) with inversion at $C_{(3)}$ by a normal S_N2 replacement, or, less probably, by an internal S_N2 replacement (cf. Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London 1953, p. 383) involving attack at $C_{(3)}$ by a phosphorus oxychloride ester derived from the 5-hydroxyl group (cf. Plattner, Petrzilka, and Lang, *loc. cit.*; Fieser *et al.*, *J. Amer. Chem. Soc.*, 1953, **75**, 4377, 4423). Dehydration of 3α-chlorocholestan-5-ol (VI) with thionyl chloride–pyridine gave *epi*cholesteryl chloride (VII).



(IV) (V) (VI) (VII)

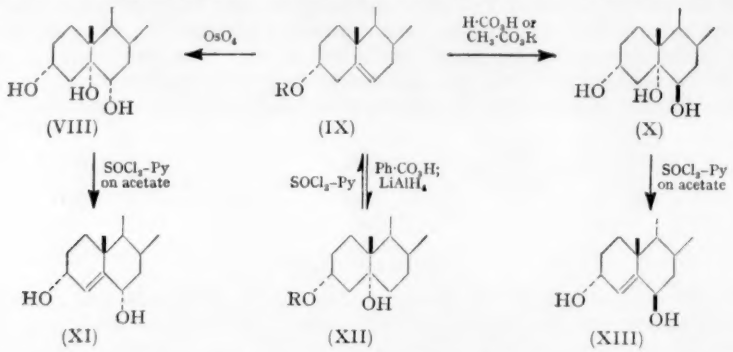
Cholestane-3α : 5-diol (XII; R = H) has been obtained previously by hydrogenation with nickel of 5-hydroxycholestan-3-one, by acid or alkaline hydrolysis (S_N2) of the 3-methanesulphonate of cholestane-3β : 5α-diol * (V) (Plattner, Fürst, Heusser, and Lang, *Helv. Chim. Acta*, 1948, **31**, 1455), and by reduction of the 4α : 5-epoxide of 3α-acetoxycholest-4-ene with lithium aluminium hydride (Plattner, Heusser, and Kulkarni, *ibid.*, 1949, **32**, 1070); we have prepared it more simply from *epi*cholesterol (IX; R = H) by conversion into the 5 : 6α-epoxide and reduction of this with lithium aluminium hydride. By treatment as the 3-monoacetate (XII; R = Ac) with thionyl chloride–pyridine, cholestane-3α : 5-diol gave *epi*cholesteryl acetate (IX; R = Ac) which appeared to be unaccompanied by 3α-acetoxycholest-4-ene.

Hydroxylation of *epi*cholesterol (IX; R = H) with osmium tetroxide furnished cholestane-3α : 5α : 6α-triol (VIII) whilst use of performic or peracetic acid yielded cholestane-3α : 5α : 6β-triol (X). Dehydration of the triols with thionyl chloride–pyridine afforded, after alkaline hydrolysis, cholest-4-ene-3α : 6α- (XI) and -3α : 6β-diol (XIII) respectively; these allylic alcohols give no colour with tetranitromethane–chloroform (cf. Ruzicka *et al.*, *Annalen*, 1929, **471**, 25; Mancera, Rosenkranz, and Djerassi, *J. Org. Chem.*, 1951, **16**, 192).

In view of work proceeding at the University of Manchester and involving 5α-hydroxysteroids with or without a $C_{(17)}$-dihydroxyacetone side-chain (Jones, Henbest, *et al.*, *J.*,

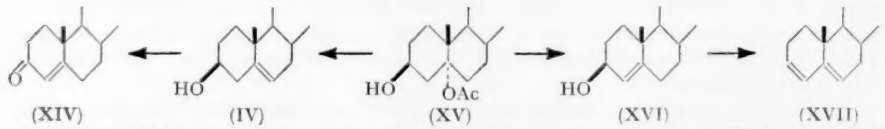
* Under alkaline conditions it would be expected that, in addition to a replacement of the 3β-methanesulphonyl group by an external hydroxyl anion with inversion at $C_{(3)}$, attack by the 5α-hydroxyl anion at the α-face of $C_{(3)}$ should lead by an internal S_N2 process to a 3α : 5α-epoxide. 3α : 5-Epoxycholestane has in fact recently been isolated from the hydrolysis product by Dr. R. B. Clayton at the University of Manchester.

1952, 4883, 4890, 4894; 1953, 2009, 2015; *Chem. and Ind.*, 1953, 945) we have investigated the mildest conditions for oxidation of 3β : 5α-diols to 5α-hydroxy-3-ketones and for dehydration of the latter to Δ^4-ketones. For this purpose cholestane-3β : 5-diol and 3β : 5 : 17α-trihydroxy*allo*pregnan-20-one were envisaged as model substances.



For oxidation of 3-hydroxy-steroids *N*-bromoacetamide appears to be the reagent of choice (Reich and Reichstein, *Helv. Chim. Acta*, 1943, **26**, 583; Gallagher *et al.*, *J. Amer. Chem. Soc.*, 1949, **71**, 3262; 1951, **73**, 184; Casanova, Shoppee, and Summers, *J.*, 1953, 2983). Cholestane-3β : 5-diol resists oxidation at 20° by *N*-bromosuccinimide in *tert.*-butanol–pyridine–water and by *N*-bromoacetamide in acetone–pyridine–water (cf. Stavely, *Fed. Proc.*, 1950, **9**, 233); but *N*-bromoacetamide in *tert.*-butanol–pyridine–water, potassium chromate in aqueous acetic acid–sodium acetate or in aqueous acetic acid, and chromium trioxide–acetic acid at 20° caused oxidation to 5-hydroxycholestan-3-one in order of increasing intensity. A similar series has been reported in a contemporaneous comparative study of oxidation of the 3α-, 7α-, and 12α-hydroxyl groups of the bile acids (Fieser and Rajagopalan, *J. Amer. Chem. Soc.*, 1950, **72**, 2307; 1951, **73**, 118).

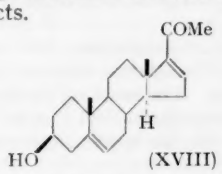
5-Acetoxycholestan-3β-ol (XV) exhibited unexpected resistance to oxidation. It was unaffected by 1% chromium trioxide–acetic acid and by potassium chromate–acetic acid at room temperature; *N*-bromoacetamide in *tert.*-butanol–pyridine–water at 25° gave cholesterol (IV) and cholesta-3 : 5-diene (XVII), whilst Oppenauer oxidation gave cholest-4-en-3-one (XIV). The resistance to oxidation appears to result from hindrance by the 5α-acetoxyl group of attack on the 3α-hydrogen atom by a proton acceptor (cf. Westheimer *et al.*, *J. Amer. Chem. Soc.*, 1949, **71**, 25); the products obtained by use of *N*-bromoacetamide appear to arise by base-catalysed 4 : 5- or 5 : 6-ionic *trans*-elimination of acetic acid, with subsequent dehydration of the allylic alcohol (XVI) and rearrangement.



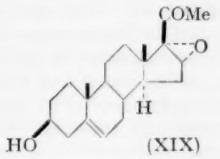
5-Hydroxycholestan-3-one exists in a second polymorphic form, m. p. 208°, $[\alpha]_D$ +40°, in addition to that of m. p. 226°, $[\alpha]_D$ +41°, described by Plattner, Fürst, Koller, and Lang (*Helv. Chim. Acta*, 1948, **31**, 1461; cf. Urushibara and Chuman, *Bull. Chem. Soc. Japan*, 1949, **22**, 69). Both forms are stable to thermal dehydration at 120°/0·01 mm. [although the epimeric 5-hydroxycoprostan-3-one undergoes dehydration at 110°/0·01 mm. (Plattner and Kulkarni, *Helv. Chim. Acta*, 1948, **31**, 1822)], but readily undergo 4 : 5-ionic *trans*-elimination to give cholest-4-en-3-one. 5α-Hydroxy-3-keto-steroids readily furnish Δ^4-3-ketones on treatment with acids (Fernholz, *Annalen*, 1934, **508**, 215; Ehrenstein *et al.*, *J. Org. Chem.*, 1941, **6**, 626, 908; 1951, **16**, 1050; 1952, **17**, 713; Plattner and Lang, *Helv. Chim. Acta*, 1944, **27**, 513; Lardon, *ibid.*, 1949, **32**, 1577) and with alkali (Plattner *et al.*, *ibid.*, 1947, **30**, 1432, 1441; 1948, **31**, 1455; 1952, **35**, 665, 2080). We have found

that 5-hydroxycholestan-3-one is unaffected by 1% hydrogen chloride in methanol at 15°, but is dehydrated to cholest-4-en-3-one by 2% hydrogen chloride in chloroform at 15°, and by larger concentrations of hydrogen chloride in methanol. Dehydration is slowly effected at 15° by aqueous methanolic 0·05N-potassium carbonate, and more rapidly by ethanolic 0·01N-sodium hydroxide or 0·015N-sodium ethoxide, and by 0·2N-potassium *tert.*-butoxide. Aluminium *tert.*-butoxide in acetone–dioxan–benzene at 15° and dimethylaniline at 194° were ineffective but hot acetic anhydride and thionyl chloride–pyridine afforded smooth and rapid dehydration. 2 : 4-Dinitrophenylhydrazine hydrochloride in hot ethanol gave the 2 : 4-dinitrophenylhydrazone of cholest-4-en-3-one (cf. Reich, Walker, and Collins, *J. Org. Chem.*, 1951, **16**, 1753), whilst semicarbazide acetate in methanol at 15° gave the semicarbazone of cholest-4-en-3-one. Use of the Girard T reagent in methanol containing 5% acetic acid also led to dehydration (cf. Prelog and Häfliger, *Helv. Chim. Acta*, 1949, **32**, 2088).

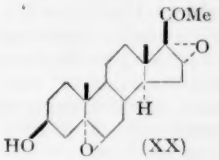
Attempts to prepare the second model substance 3β : 5 : 17α-trihydroxy*allo*pregnan-20-one were unsuccessful, and had to be discontinued owing to external circumstances. 3β-Hydroxypregna-5 : 16-dien-20-one (XVIII) was quantitatively converted by alkaline hydrogen peroxide into the 16α : 17α-epoxide (XIX), which by treatment with excess of perbenzoic acid in benzene at 15° gave the 5 : 6α-16α : 17α-diepoxide (XX) accompanied by an unidentified substance. A crystalline 20-ketal of the diepoxide (XX) could not be obtained; direct reduction of the bisepoxide with lithium aluminium hydride, or by use of hydrogen bromide followed by debromination with Raney nickel, failed to give crystalline products.



(XVIII)



(XIX)



(XX)

An alternative approach involving peroxidation of the 17 : 20-enol acetate of 3β-hydroxypregn-5-en-20-one was unsatisfactory.

Experimental

For general experimental details see *J.*, 1953, 3683. $[\alpha]_D$ are in $CHCl_3$; ultra-violet absorption spectra were determined in EtOH on a Unicam SP. 500 with corrected scale, and infra-red absorption spectra on a Perkin-Elmer double-beam instrument.

Dehydration of Cholestan-5-ol.—Cholest-5-ene was converted by treatment with perbenzoic acid into a mixture of 5 : 6α-epoxycholestane and 5 : 6β-epoxycoprostane, which by reduction with lithium aluminium hydride gave a mixture of cholestan-5- and -6β-ol. This was acetylated (acetic anhydride–pyridine at 20°) and then by chromatography furnished (pentane as eluant) cholestan-5-ol, m. p. 107—109°, $[\alpha]_D$ +12·5° (*c*, 2·1), and [benzene–pentane (1 : 9)] cholestan-6β-yl acetate, which by alkaline hydrolysis gave cholestan-6β-ol, m. p. 79—80° (cf. Shoppee and Summers, *J.*, 1952, 3361). Dehydration of cholestan-5-ol (100 mg.) with thionyl chloride (1 c.c.) in pyridine (5 c.c.) at 20° furnished an oil, $[\alpha]_D$ +3·5°, giving an intense yellow colour with tetranitromethane–chloroform. The value of $[\alpha]_D$ corresponds to an approximately equimolecular mixture of cholest-4-ene ($[\alpha]_D$ +65°) and -5-ene ($[\alpha]_D$ −56°); filtration of a pentane solution through a column of aluminium oxide and a single elution of the column with pentane gave two fractions with $[\alpha]_D$ +8° and +1° respectively. A repetition gave a similar result.

Dehydration of Cholestane-3β : 5-diol and its 3-Monoacetate.—The monoacetate (500 mg.) in pyridine (15 c.c.) was treated at 0° with thionyl chloride (5 c.c.); the solution became deep red, and after 10 min. at 15° was poured into ice-water. The product by chromatography gave cholesteryl acetate, m. p. 112—115°, mixed m. p. 114°, as the sole crystalline product. The diol (1 g.) by similar treatment gave cholesteryl sulphite (720 mg.), m. p. 190—192° after crystallisation from dioxan.

The diol (1 g.) in pyridine (25 c.c.) was treated gradually with phosphorus oxychloride (10 c.c.) at 15°. After 1 hr. at 15°, the excess of reagent and the solvent were removed in a vacuum at 40°. The product was worked up in the usual way, and crystallised when rubbed with methanol; recrystallisation from ether–methanol gave 3α-*chlorocholestan-5-ol* (680 mg.), m. p. 118—119°

[Found (after drying at 60°/0·03 mm. for 3 hr.) : C, 76·7; H, 11·1. $C_{27}H_{47}OCl$ requires C, 76·6; H, 11·1%]; it gave no colour with tetranitromethane, and furnished a red colour in the Rosenheim test only after 0·5 hr. 3α-Chlorocholestan-5-ol (100 mg.) in pyridine (2·5 c.c.) was treated at 0° with thionyl chloride (0·5 c.c.); after 10 min. at 15°, the mixture was poured on ice and worked up in the usual way. The resultant yellow oil (94 mg.) by chromatography on neutralised aluminium oxide (3 g.) and elution with pentane gave 3α-chlorocholest-5-ene (*epi*cholesteryl chloride) (59 mg.), m. p. and mixed m. p. 105—107·5°. The diol, by treatment with phosphorus pentachloride in chloroform at 0° in presence of calcium carbonate gave unsaturated material which failed to crystallise despite attempted chromatographic purification. By use of anhydrous copper sulphate (5 g.) in boiling benzene (100 c.c.) for 3·5 hr., the diol (1 g.) gave an oil (875 mg.), which crystallised when rubbed with methanol; recrystallisation from methanol–ether gave cholesta-3 : 5-diene, m. p. 80°, $\lambda_{max.}$ 235, log ε 4·25, giving an immediate positive reaction in the Rosenheim test.

5 : 6α-*Epoxycholestan*-3α-*ol.*—*epi*Cholesterol (1·1 g.) in chloroform (25 c.c.) was treated with perbenzoic acid (1·1 mol.) in chloroform overnight at −10°. The solution was washed successively with potassium iodide, 0·01N-sodium thiosulphate, sodium hydrogen carbonate solution, and water, and the product (1 g.) crystallised from acetone–methanol, to give 5 : 6α-*epoxycholestan*-3α-*ol* in needles, m. p. 125—128°, $[\alpha]_D$ −44° (*c*, 0·58) [Found (after drying at 60°/0·01 mm. for 3 hr.) : C, 80·4; H, 11·9. $C_{27}H_{46}O_2$ requires C, 80·5; H, 11·5%].

Cholestane-3α : 5-*diol.*—5 : 6α-Epoxycholestan-3α-ol (246 mg.) was reduced with lithium aluminium hydride in ether under reflux. Treatment with ice-cold N-sulphuric acid and working up gave cholestane-3α : 5-diol (227 mg.) as shining plates (from methanol), m. p. 199°, $[\alpha]_D$ +18° (*c*, 1·00). Acetylation with acetic anhydride–pyridine at 20° gave the 3α-monoacetate, m. p. 132—133° (cf. Plattner *et al.*, *Helv. Chim. Acta*, 1948, **31**, 1454).

Dehydration of Cholestane-3α : 5-*diol* 3-*Monoacetate.*—The 3α-monoacetate (500 mg.) in pyridine (15 c.c.) was treated with thionyl chloride (5 c.c.) at 0°; the solution became deep red and, after 10 min. at 15°, was poured into ice-water, and worked up. The resulting oil, dissolved in pentane, was chromatographed on aluminium oxide, and gave *epi*cholesteryl acetate, plates (from methanol), m. p. 82°, undepressed by admixture with a genuine specimen, as the sole crystalline product.

Cholestane-3α : 5 : 6α-*triol.*—Cholest-5-en-3α-ol (*epi*cholesterol) (500 mg.) in ether (10 c.c.) was treated with a solution of osmium tetroxide (300 mg.) in ether (50 c.c.) containing pyridine (0·5 c.c.). After 14 days at 15°, ether was removed by evaporation and the residue shaken with 2N-potassium hydroxide. The product was extracted with ether, and the extract washed with aqueous sodium hydrogen sulphite and with water, dried, and evaporated to give a gel. This crystallised on trituration with solvents, and recrystallisation from acetic acid gave *cholestane*-3α : 5 : 6α-*triol* (381 mg.), m. p. 168—172°, $[\alpha]_D$ +13° (*c*, 1·50) [Found (after drying at 70°/0·02 mm. for 6 hr.) : C, 77·0; H, 11·55. $C_{27}H_{48}O_3$ requires C, 77·1; H, 11·5%]. The acetate was prepared by using acetic anhydride–pyridine at 15°, but could not be obtained crystalline after chromatographic purification and sublimation.

Cholestane-3α : 5 : 6β-*triol.*—Cholest-5-en-3α-ol (*epi*cholesterol) (1·62 g.) in acetic acid (50 c.c.) was treated with hydrogen peroxide (7 c.c. of 100-vol.), and the mixture heated at 70° for 2·5 hr. After dilution with water, the product was extracted with ether and worked up to give an oil, which was hydrolysed with N-methanolic potassium hydroxide under reflux for 1 hr. The product (1·2 g.), isolated in the usual way, failed to crystallise; attempted crystallisation from a large variety of solvents gave gels. Acetylation with acetic anhydride–pyridine at 15° gave *cholestane*-3α : 5 : 6β-*triol* 3-*monoacetate*, which crystallised from ethyl acetate–methanol without difficulty, having m. p. 188—190°, $[\alpha]_D$ −22° (*c*, 1·10) [Found (after drying at 70°/0·02 mm. for 6 hr.) : C, 75·3; H, 10·8. $C_{29}H_{50}O_4$ requires C, 75·3; H, 10·8%]. This acetate was also obtained from *epi*cholesterol by use of performic acid, hydrolysis, and reacetylation.

Cholest-4-*ene*-3α : 6α-*diol.*—The amorphous 3α : 5 : 6α-triol acetate by treatment with thionyl chloride in pyridine at 0° in the usual manner furnished a product which was hydrolysed with hot N-methanolic potassium hydroxide for 1 hr. Crystallisation from acetone gave *cholest*-4-*ene*-3α : 6α-*diol*, m. p. 166—167°, $[\alpha]_D$ +81° (*c*, 1·4), giving no colour with tetranitromethane [Found (after drying at 70°/0·02 mm. for 6 hr.) : C, 80·8; H, 11·4. $C_{27}H_{46}O_2$ requires C, 80·55; H, 11·5%].

Cholest-4-*ene*-3α : 6β-*diol.*—The 3α : 5 : 6β-triol acetate, m. p. 188° (500 mg.), in pyridine (15 c.c.) was treated with thionyl chloride (5 c.c.) at 0°; the solution at once became deep red, and after 15 min. at 15° was poured into ice-cold 2N-hydrochloric acid. The product, isolated in the usual way, was hydrolysed with hot N-methanolic potassium hydroxide for 1 hr. Crystal-

lisation from ethyl acetate afforded *cholest-4-ene-3α : 6β-diol*, m. p. 220—223°, insoluble in chloroform, giving no colour with tetranitromethane [Found (after sublimation at 190°/0·005 mm.): C, 80·4; H, 11·4%].

Oxidation of Cholestane-3β : 5-diol.—Owing to the proximity of the m. p. of the diol and of the two forms of 5-hydroxycholestan-3-one, the identity of material was confirmed by treatment with methanolic 2 : 4-dinitrophenylhydrazine which rapidly converts 5-hydroxycholestan-3-one into the red dinitrophenylhydrazone, m. p. 235°, of cholest-4-en-3-one.

(*a*) The diol (1 g.), dissolved in *tert.*-butanol (75 c.c.) and water (25 c.c.), was treated with *N*-bromosuccinimide at 10° for 20 hr.; the product was unaltered diol, m. p. and mixed m. p. 222—224°, $[\alpha]_D$ +17°, after crystallisation from ethyl acetate.

(*b*) The diol (0·5 g.), dissolved in acetone (100 c.c.) and pyridine (2·5 c.c.), was treated with *N*-bromoacetamide (0·4 g.) at 25° for 50 hr.; the product was unchanged diol, m. p. 218—222°, after crystallisation from acetone.

(*c*) The diol (1 g.), dissolved in *tert.*-butanol (150 c.c.), pyridine (2·5 c.c.), and water (2·5 c.c.), was treated with *N*-bromoacetamide (0·75 g.) at 25° for 72 hr.; the product was 5-hydroxycholestan-3-one, which crystallised from acetone in two forms: m. p. 208—210°, and m. p. 229—231°.

(*d*) (*e*) (*f*) (*g*). The diol (1 g.) by oxidation (*d*) with a solution of potassium chromate (3·2 g. in 10 c.c. of water) in acetic acid (200 c.c.) containing sodium acetate trihydrate (2 g.) at 15° for 20 hr., (*e*) with a solution of potassium chromate (2 g. in 5 c.c. of water) in acetic acid (100 c.c.) at 15° for 20 hr., (*f*) with a 1% solution of chromium trioxide in 98% acetic acid at 18° for 17 hr., or (*g*) in anhydrous acetic acid gave 5-hydroxycholestan-3-one, m. p. 208°, $[\alpha]_D$ +42°; in experiment (*f*), the second form, m. p. 229—231°, $[\alpha]_D$ +41°, was also encountered.

(*h*) The diol (0·5 g.), dissolved in dioxan (20 c.c.) and acetone (30 c.c.), was treated with a solution of aluminium *tert.*-butoxide (2 g.) in benzene (70 c.c.) under reflux for 20 hr. The product, after chromatographic purification, afforded cholest-4-en-3-one (416 mg.), m. p. 81—82° (dinitrophenylhydrazone, m. p. 235°).

Oxidation of 5-Acetoxycholestan-3β-ol.—This was obtained from cholestane-3β : 5-diol, by conversion with acetyl chloride–dimethylaniline in boiling chloroform into the 3β : 5-diacetate, m. p. 140—141°, and partial hydrolysis with N-ethanolic potassium hydroxide at 10° for 20 hr.; it had m. p. 160—161°, $[\alpha]_D$ +30° (*c*, 1·1) (cf. Plattner *et al.*, *Helv. Chim. Acta*, 1944, **27**, 513, 1872).

(*a*) 5-Acetoxycholestan-3β-ol (550 mg.), dissolved in acetic acid (25 c.c.), was treated with a 2% solution of chromium trioxide in 98% acetic acid (25 c.c.) at 20° for 20 hr. The product (500 mg.), isolated in the usual way, crystallised from methanol in needles, m. p. 160—161°, and consisted of unchanged material; the alkaline washings by acidification gave traces of a solid acid. Potassium chromate in acetic acid at 20° was likewise ineffective.

(*b*) 5-Acetoxycholestan-3β-ol (1 g.), dissolved in *tert.*-butanol (100 c.c.), pyridine (5 c.c.), and water (5 c.c.), was treated with *N*-bromoacetamide (1 g.) at 20° for 24 hr. The pale yellow solution was diluted with ether, washed with sodium thiosulphate solution, and worked up in the usual way. The product was chromatographed on a column of neutralised aluminium oxide (30 g.) prepared in pentane. Elution with pentane and benzene–pentane (1 : 9) gave cholesta-3 : 5-diene (143 mg.) (possibly containing traces of cholesta-2 : 4-diene), m. p. 78°, mixed m. p. 78—79°, $[\alpha]_D$ −102° (*c*, 1·32), giving an immediate red colour in the Rosenheim test. Use of benzene and ether–benzene mixtures gave only oils, but elution with ether and chloroform–ether (1 : 1) gave cholesterol (215 mg.), m. p. 148°, characterised as cholesteryl acetate, m. p. 115°.

(*c*) 5-Acetoxycholestan-3β-ol (400 mg.), dissolved in dioxan (18 c.c.) and acetone (25 c.c.), was heated with a solution of aluminium *tert.*-butoxide (2 g.) in benzene (70 c.c.) for 22 hr. The product (352 mg.), by chromatography on neutralised aluminium oxide (12 g.) and elution with benzene–pentane mixtures, gave cholest-4-en-3-one (256 mg.), m. p. 79—82° (2 : 4-dinitrophenylhydrazone, m. p. 235°), and by use of ether–benzene mixtures starting material (70 mg.), m. p. 161°.

5-Hydroxycholestan-3-one.—Both forms, m. p. 208—212°, $[\alpha]_D$ +40° (*c*, 1·5), and m. p. 229—231°, $[\alpha]_D$ +41° (*c*, 1·4) [Found (after drying at 100°/0·01 mm. for 2 hr.): C, 80·3; H, 11·2. Calc. for $C_{27}H_{46}O_2$: C, 80·5; H, 11·5%], were unchanged after 6 hr. at 120°/0·01 mm; sublimation occurred at 185°/0·01 mm. to give a product melting over the range 206—231°, $[\alpha]_D$ +41° (*c*, 1·9). Both forms by treatment with methanolic 2 : 4-dinitrophenylhydrazine hydrochloride gave the red dinitrophenylhydrazone, m. p. 238°, of cholest-4-en-3-one. Attempts to prepare the 5-acetate by use of keten or of the acetyl chloride–dimethylaniline procedure were unsuccessful (cf. Plattner *et al.*, *Helv. Chim. Acta*, 1948, **31**, 1461).

Dehydration of 5-Hydroxycholestan-3-one.—(*a*) The ketol (m. p. 208°; 435 mg.) was dissolved in methanol (100 c.c.) containing 1% of hydrogen chloride at 20° and set aside for 20 hr. After neutralisation with solid sodium hydrogen carbonate, methanol was removed in a vacuum, and the residue crystallised from acetone, to give the unchanged ketol (400 mg.), m. p. 208°.

(*b*) A solution of the ketol (m. p. 208°; 230 mg.) in pure dry chloroform (10 c.c., free from ethanol) containing 2% of hydrogen chloride was allowed to stand at 15° for 20 hr. The product, isolated in the usual way, was a colourless oil (200 mg.), which crystallised when rubbed with methanol and consisted of cholest-4-en-3-one, m. p. and mixed m. p. 80—82°.

(*c*) The ketol (m. p. 231°; 500 mg.), dissolved in acetone (20 c.c.) and dioxan (10 c.c.), was treated with a solution of aluminium *tert.*-butoxide (2·5 g.) in benzene (70 c.c.) at 15° for 18 hr. The product (490 mg.) was recrystallised from ethyl acetate, to give the starting material, m. p. and mixed m. p. 230—232°. The ketol was unchanged by refluxing dimethylaniline for 6 hr., but dehydration to cholest-4-en-3-one was effected at 15° by aqueous-methanolic 0·05N-potassium carbonate, by 0·01N-sodium hydroxide and 0·015N-sodium ethoxide in ethanol, and by 0·2N-potassium *tert.*-butoxide in *tert.*-butanol.

Both forms of the ketol were dehydrated by hot acetic anhydride (5 min.), and by thionyl chloride–pyridine at 15° (30 min.). Use of 2 : 4-dinitrophenylhydrazine hydrochloride in ethanol gave cholest-4-en-3-one 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 238—241°, whilst semicarbazide acetate in methanol at 50° for 2 min. and then at 15° for 1·5 hr. gave an 80% yield of cholest-4-en-3-one semicarbazone, m. p. 250—251° (decomp.), after recrystallisation from acetone–methanol [Found (after drying at 50°/0·01 mm. for 3 hr.) : N, 9·65. Calc. for $C_{28}H_{47}ON_3$: N, 9·5%] [Diels and Abderhalden, *Ber.*, 1904, **37**, 3092, give m. p. 234° (decomp.)].

(*d*) The ketol (m. p. 231°; 500 mg.) in ethanol (50 c.c.) was refluxed with Girard's reagent T (600 mg.) and acetic acid (2·5 c.c.) for 1·5 hr. The mixture was cooled to 15° by addition of ice, a solution of anhydrous sodium carbonate (1 g.) added, and the whole extracted quickly twice with ether. The combined extracts were washed with ice-water, dried, and evaporated, to give the unchanged ketol (50 mg.), m. p. 230—231° after recrystallisation from acetone. The alkaline liquor, together with the aqueous washings, were acidified with 2N-sulphuric acid, warmed to 40°, and set aside at 20° for 3 hr. Extraction with ether gave an oil (350 mg.) which crystallised, and by chromatographic purification furnished cholest-4-en-3-one (300 mg.), m. p. 81—82°, $[\alpha]_D$ +89° (*c*, 2·5).

16α : 17α-*Epoxy*-3β-*hydroxypregn*-5-*en*-20-*one*.—3β-Hydroxypregna-5 : 16-dien-20-one (3 g.; $\lambda_{max.}$ 238 mμ, log ε 4·03; $\lambda_{max.}$ 208 mμ, log ε 3·69), dissolved in methanol (300 c.c.), was treated with 4N-sodium hydroxide (6 c.c.) followed by 30% hydrogen peroxide (12 c.c.). The mixture was warmed to 30° for 0·5 hr., and then kept at 5° until examination of the ultra-violet absorption of a sample showed that the band at 238 mμ had disappeared (20 hr.). The product by recrystallisation from methanol gave 16α : 17α-epoxy-3β-hydroxypregn-5-en-20-one (2·5 g.), m. p. 190°, $\lambda_{max.}$ 208 mμ, log ε 3·87 [2 : 4-dinitrophenylhydrazone, yellow needles, m. p. 179—182°] (cf. Julian *et al.*, *J. Amer. Chem. Soc.*, 1950, **72**, 5145).

5 : 6α-16α : 17α-*Diepoxy*-3β-*hydroxy*allo*pregnan*-20-one.—The 16α : 17α-epoxide (5 g.), dissolved in benzene (200 c.c.), was treated with a solution of perbenzoic acid (0·0317 mg./c.c.) in benzene (80 c.c.) at 15° for 1 week. During this period the band at 208 mμ became reduced in intensity but did not disappear; an excess of perbenzoic was always present, and crystals (2·96 g.) gradually separated. Recrystallisation from acetone gave 5 : 6α-16α : 17α-*diepoxy*-3β-*hydroxy*allo*pregnan*-20-*one*, m. p. 214—216°, $\lambda_{max.}$ 207 mμ, log ε 3·42, with bands in the infra-red at 3610 and 3480 cm.$^{-1}$ (OH), 1694 cm.$^{-1}$ (CO), and 1648, 1300, and 912 (two epoxide groups), which appeared tenaciously to retain solvent [Found (after drying at 100°/0·01 mm. for 6 hr. : C, 72·5; H, 8·8. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·7%] (2 : 4-dinitrophenylhydrazone, yellow prisms, m. p. 195—197°). A second unidentified substance, m. p. 148—149° (Found : C, 69·7; H, 8·8%) with broad bands in the infra-red at 3570 and 3420 (>1OH), 1694 (CO), and at 1635, 1300, and 900 cm.$^{-1}$ (one epoxide group), obtained from the mother liquors, cannot be a 16α : 17α-epoxy-3β : 5 : 6-triol 6-monobenzoate since it was unchanged by hot 5% methanolic potassium hydroxide.

Two of us (A. J. F. and G. H. R. S.) acknowledge the financial support of Glaxo Laboratories Ltd. and of the Department of Scientific and Industrial Research respectively. We thank Glaxo Laboratories Ltd. for a gift of cholesterol, British Drug Houses Ltd. for a gift of pregnenolone, and Dr. G. Rosenkranz of Syntex Ltd., Mexico City, for a gift of 3β-hydroxypregna-5 : 16-dien-20-one.

University College, Swansea, University of Wales. [*Received, November 17th*, 1953.]

Acid-catalysed Racemisation of 1-*Methylheptyl Acetate.*

By M. P. Balfe, W. H. F. Jackman, and J. Kenyon.

[Reprint Order No. 4892.]

1-Methylheptyl acetate racemises when heated, in acetic acid solution, with strong acids.

Other esters of octan-2-ol, when heated with acetic acid in presence of strong acids, undergo some racemisation and yield extensively racemised 1-methylheptyl acetate. The reaction of 1-methylheptyl toluene-*p*-sulphonate with acetic acid occurs mainly with inversion of configuration.

Experiments on the racemisation and reactions of 1-methylheptyl esters in acetic acid solution, which were referred to in a preliminary note (Balfe and Kenyon, *Nature*, 1941, **148**, 196), are summarised in Tables 1 & 2. These experiments arose from an investigation of the reaction of optically active 1-methylheptyl toluene-*p*-sulphonate with acetic acid which was complicated by the continuous racemisation of the resulting acetate by the toluene-*p*-sulphonic acid formed along with it. Under conditions which retard this racemisation, *e.g.* by extensively diluting the reactants with benzene (cf. the sixth and seventh experiments in Table 1), 1-methylheptyl toluene-*p*-sulphonate reacts with acetic acid to yield 1-methylheptyl acetate with 80% inversion of configuration.

Table 1. *Racemisation of* 1-*methylheptyl acetate* [all quantities are given in mols. per mol. of ester].

Acetic acid	Strong acid	Amount	Diluent	Amount	Hours on steam-bath	% Racemn. of recovered ester	$t_{\frac{1}{2}}$ racemn. hr.
50	—	0	—	0	48	0	—
18	$Me{\cdot}C_6H_4{\cdot}SO_3H$	1	—	0	12	18	—
18	,,	1	—	0	36	58	—
16	,,	1	H_2O	5	12	6	—
7	,,	1	—	0	24	96	—
7	,,	1	C_6H_6	45	24	8	—
2	,,	1	,,	11	12	8	—
2	,,	1	,,	11	36	41	—
2	,,	1	AcOEt	10	12	0	—
2	,,	1	,,	10	36	4	—
8	,,	1	—	0	12	2	—
18	H_2SO_4	0·5	—	0	24	100	3
16	,,	0·5	H_2O	5	24	64	16
7·5	,,	0·5	—	0	24	98	—
2	,,	0·5	Ac_2O	9	24	62	12
2	,,	0·5	COMeEt	10	24	50	24
2	,,	0·5	Dioxan	10	24	34	35 *
0	,,	0·5	,,	12	24	39	40 *
18	,,	0·5	—	0	3	53	3
14	,,	0·5	$MeNO_2$	4·5	3	43	4
11	,,	0·5	,,	9	3	50	3
8	,,	0·5	,,	13	3	69	2
4	,,	0·5	,,	18	3	83	1
18	,,	0·25	—	0	24	64	17
16	HCl	1	H_2O	5	12	69	—

* Extrapolated.

Hughes, Ingold, and Masterman (*J.*, 1939, 840) showed that 1-methylheptyl acetate, prepared by acid-catalysed esterification of (+)-octan-2-ol during 2—5 hours at 100°, is 30% racemic. We find that when the (+)-acetate is heated with acetic acid and sulphuric acid in proportions corresponding to the final concentrations of that experiment, the acetate is 7% racemised after 2·5 hours and 15% racemised after 5 hours. The conclusion of Hughes, Ingold, and Masterman (*loc. cit.*) that some racemisation occurs during the acid-catalysed esterification therefore remains valid though part of the racemisation which they observed may have occurred subsequently to the formation of the ester.

TABLE 2. *Formation of* 1-*methylheptyl acetate by the action of acetic acid* (*in the presence of a strong acid*) *on other* 1-*methylheptyl esters* [quantities are given in mols. per mol. of ester].

Acetic acid	Strong acid	Amount	Diluent or other reactant	Amount	Hr. on steam-bath	Original ester % recovd.	Original ester % racemn.	Acetate formed % isolated	Acetate formed % racemn.
			1-Methylheptyl benzoate.						
18	$Me{\cdot}C_6H_4{\cdot}SO_3H$	1	$Ph{\cdot}CO_2H$	2	12	—	9	25	65 †
18	H_2SO_4	0·5	,,	2	12	30	15	24	99 *
18	,,	0·5	,,	2	24	12	39	32	99 *
18	,,	0·5	,,	2	36	12	62	37	99 *
18	,,	0·25	,,	2	12	—	2	—	62 *
18	,,	0·12	,,	2	12	—	0	—	62 *
0	,,	0·5	,,	2	24	—	5	—	—
			Dioxan	12					
			1-Methylheptyl o-nitrobenzoate.						
18	$Me{\cdot}C_6H_4{\cdot}SO_3H$	1	$NO_2{\cdot}C_6H_4{\cdot}CO_2H$	2	12	—	21	25	96 *
			1-Methylheptyl hydrogen phthalate.						
18	,,	1	$C_6H_4(CO_2H)_2$	2	12	—	0	18	58 †

* Inverted configuration. † Retained configuration.

EXPERIMENTAL

Racemisation of 1-*Methylheptyl Acetate.*—The maximum reported rotatory power for the (+)-ester, from (+)-octan-2-ol, is $[\alpha]_D^{16}$ +6·90° (Houssa and Phillips, *J.*, 1929, 2510). Since, however, ester of varying optical purity was used the results of the experiments are recorded as % racemisation, *i.e.*, loss in rotatory power as % of original rotatory power. Approximately 3-g. portions of the acetate were heated on the steam-bath with the reactants and solvents and for the periods stated in Table 1. The maximum duration of continuous heating was limited by circumstances to 12 hr. and in more prolonged experiments two or more separate periods of heating were required, with intermediate cooling to room temp. during some 12 hr. It was established that 1-methylheptyl acetate does not undergo racemisation at room temperature under any of the experimental conditions used. The reaction mixture was finally diluted with water and extracted with ether, and the extract washed with water and sodium hydrogen carbonate solution until free from acid, dried with potassium carbonate, and concentrated. The residual 1-methylheptyl acetate was redistilled (b. p. *ca.* 90°/20 mm.) to constant refractive index (n_D^{20} 1·415—1·416), and the rotatory power of the homogeneous product observed. Where times of half-racemisation were recorded, larger amounts of ester were used and the equivalents of 3 g. of ester were withdrawn at 3-hr. intervals of heating for recovery of the ester as described above: $t_{\frac{1}{2}}$ was read from the plot of % racemisation against time. The solution darkened too rapidly to allow of continuous polarimetric observation.

Other esters were prepared by the reaction of optically pure octan-2-ol with the appropriate acid chloride or anhydride in presence of pyridine, and % racemisation was calculated on the assumption that the esters were optically pure (Table 2).

In all experiments, % racemisation was calculated on the assumption that optically pure 1-methylheptyl acetate has α_D^{17-22} +6·5° (*l*, 1) (Pickard and Kenyon, *J.*, 1911, **99**, 60; Hughes, Ingold, and Masterman, *loc. cit.*).

Racemisation of 1-*methylheptyl acetate* (cf. Hughes, Ingold, and Masterman, *loc. cit.*). A solution of the ester (10·3 g.; α_D^{16} +6·16°) in acetic acid (32·7 g.), containing water (1·3 g.) and sulphuric acid (0·59 g.), was heated in boiling water. Portions were withdrawn at intervals, and the ester recovered as previously described. The rotatory powers, α_D^6, of the recovered ester were: after 1·3 hr. 5·85°, 2·6 hr. 5·70°, 5·4 hr. 5·24°.

Reactions of 1-*Methylheptyl Toluene*-p-*sulphonate.*—The maximum observed rotatory power of this ester is α_D^{22} −7·41° (*l*, 1): this value was employed to calculate the optical purity of the various specimens used: α_D^{16} +6·5° (*l*, 1) was used to calculate the optical purity of 1-methylheptyl acetate formed. From these two figures the % racemisation during reaction was calculated.

(i) *With sodium acetate in acetic acid.* The toluene-*p*-sulphonate (11·4 g.) (α_D^{22} +7·15°; *l*, 1) with sodium acetate (6·6 g., 2 mols.) in acetic acid (19·2 g., 8 mols.) was heated for 36 hr. on the steam-bath. The resulting acetate (1·9 g.), isolated as described above, had α_D^{20} −4·00°, *i.e.*, inversion of configuration and 35% racemisation had occurred.

(ii) *With acetic acid; no diluent.* A solution of the toluene-*p*-sulphonate (11·4 g.) (α_D^{22} +6·3°; *l*, 1) in acetic acid (19·2 g., 8 mols.) was heated on the steam-bath for 12 hr. The acetate obtained (1·8 g.) had α_D^{21} −1·25°, *i.e.* inversion of configuration and 80% racemisation had occurred.

(iii) *With acetic acid diluted with benzene.* The toluene-*p*-sulphonate (11·4 g.; α_D^{18} −5·2°) in acetic acid (19·2 g., 8 mols.) and benzene (114 c.c.) was heated on the steam-bath for 48 hr. The resulting acetate (1·7 g.) had α_D^{18} +2·9°, *i.e.*, inversion of configuration and 40% racemisation had occurred.

Thanks are expressed to Imperial Chemical Industries Limited for a grant.

BATTERSEA POLYTECHNIC, LONDON, S.W.11. [*Received, December 15th*, 1953.]

The Constitution of Conessine. Part VII. Degradation of Some Reduced Quinoline and Indole Bases.*

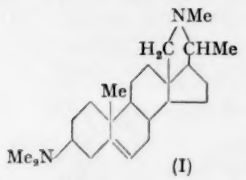
By B. BAILEY, R. D. HAWORTH, and J. MCKENNA.

[Reprint Order No. 4747.]

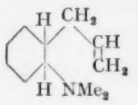
cis- and *trans*-Decahydroquinoline, *cis*-octahydro-1-methylindole, *cis*(?)-octahydro-2-methyl*iso*indole, and homologues thereof have been degraded by the Hofmann and the Emde procedure; in general the reactions take the expected course. The acetic acid cyclisation of methine bases derived from the heterocyclic amines is described.

RECENT investigations by Haworth, McKenna, and their collaborators (*J.*, 1953, 1102, 1110, 1115) on the constitution of the steroidal alkaloid conessine have led to the proposal of formula (I); the positions of the double bond and the dimethylamino-group are now well established, and the heterocyclic ring arrangement is probably correct. The Hofmann and the Emde degradation reactions of quaternary ammonium salts have been of considerable utility in elucidating the chemistry of conessine, and, in view of the characteristic behaviour of the alkaloid, it was decided at an early stage of the investigation to carry out parallel degradations with simpler heterocyclic amines. Moreover, it has been found (Haworth, McKenna, Powell, and Woodward, *J.*, 1951, 1736; Favre, Haworth, McKenna, Powell, and Whitfield, *loc. cit.*, p. 1115) that unsaturated methine bases of the type $\underline{CH{=}CH_2}\text{–}NMe_2$ derived from conessine are readily cyclised on treatment with glacial acetic acid or hot hydroxylic solvents with the production of related quaternary salts $\{\underline{CH_2{-}CH_2}\text{–}NMe_2^+\}\,X^-$ (X = OAc or OH), and it was therefore planned to examine simpler unsaturated methines from the same standpoint.

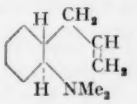
The Hofmann degradation of *cis*- and *trans*-decahydroquinolines has been described by Fujise (*Sci. Papers Inst. Phys. Chem. Res., Tokyo*, 1928, **8**, 185) who found that each base yielded an unsaturated methine, the dihydro-derivatives from which were not identical; formulæ (II) and (III) were therefore suggested for these methines. Confirmation in the



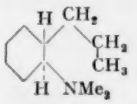
(I)



(II)



(III)



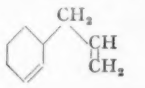
(IV)

case of the methine base (III) derived from *trans*-decahydroquinoline was subsequently (*ibid.*, 1929, **10**, 83) obtained by identification of its dihydro-derivative as *trans-NN*-dimethyl-2-propyl*cyclo*hexylamine (IV). We have confirmed Fujise's results and find that each methine base on Emde reduction yields allyl*cyclo*hexane, the constitution of which

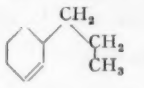
* Part VI, *J.*, 1953, 1115.

follows from its oxidation to *cyclo*hexylacetic acid. Hofmann decomposition of the methine bases (II) and (III) yields doubly unsaturated hydrocarbons [probably identical, and probably 3-allyl*cyclo*hexene (V)] in which the double bonds are not in conjugation. Hofmann decomposition of *trans-NN*-dimethyl-2-propyl*cyclo*hexylamine (IV) yields 3-propyl*cyclo*hexene (VI), the constitution of which was proved by oxidation with permanganate to heptane-1 : 4-dicarboxylic acid. Hofmann decomposition of the base (IV) had previously been investigated by Fujise (*loc. cit.*) who showed that the product was not the known 1-propyl*cyclo*hexene; this isomer would not in any case be expected on general considerations (not the least substituted ethylene) and it would probably have yielded a monobasic keto-acid on oxidation.

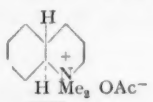
When the methine base (III) derived from *trans*-decahydroquinoline was boiled with acetic acid it yielded a mixture of quaternary acetates containing a little *trans*-decahydro-1-methylquinoline methoacetate (VII), isolated as iodide by chromatography. The remainder of the cyclised acetates probably consisted of a mixture of the epimeric forms of *trans*-octahydro-1 : 2-dimethylindole methoacetate (VIII; epimeric at $C_{(2)}$) since selenium



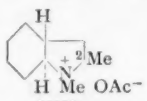
(V)



(VI)



(VII)

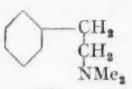


(VIII)

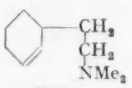
dehydrogenation gave 2-methylindole in addition to some quinoline. Hofmann degradation of the quaternary mixture gave back the parent methine (III). No cyclisation of (III) resulted from boiling in alcohol or aqueous glycol, but with aqueous potassium hydroxide a little quaternary product was obtained and isolated as methiodide.

The methine base (II) derived from *cis*-decahydroquinoline was also found to cyclise readily in acetic acid, but the products were not investigated.

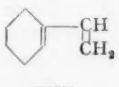
(IX)



(X)

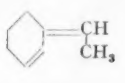


(XI)

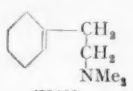


(XII)

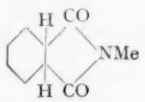
Barltrop, King, and Walley (*J.*, 1945, 277) submitted *cis*-octahydro-1-methylindole (IX) to Hofmann degradation and obtained a β-dimethylaminoethyl*cyclo*hexene which yielded 2′-dimethylaminoethyl*cyclo*hexane (X) on catalytic hydrogenation. We have confirmed the structure of the dihydromethine (X) by Hofmann degradation to vinyl*cyclo*hexane, which gave hexahydrobenzoic acid on permanganate oxidation. Baltrop, King, and Walley did not identify the position of unsaturation in their unsaturated methine, but formula (XI), which appears likely on general grounds (least substituted ethylene), has been confirmed by Emde reduction of the base followed by oxidation of the resulting 3-ethyl*cyclo*hexene to 2-ethyladipic acid. Further Hofmann degradation of the methine (XI) gave an unsaturated hydrocarbon C_8H_{12} with two double bonds in conjugation; the ultra-violet absorptions of this hydrocarbon (at 2295 and 2340 Å) excludes a *cyclo*hexadiene structure and indicate formulæ (XII) or (XIII) or a mixture. Treatment of the methine (XI) with glacial acetic acid gave a mixture of *cis*- and *trans*-octahydro-1-methylindole methoacetates, characterised as the corresponding picrates. In hot alkaline ethylene glycol, (XI) was



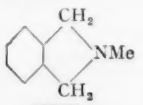
(XIII)



(XIV)



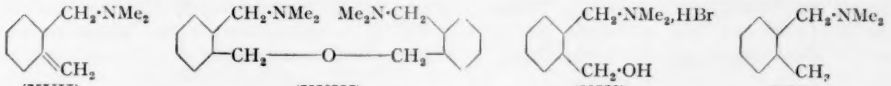
(XV)



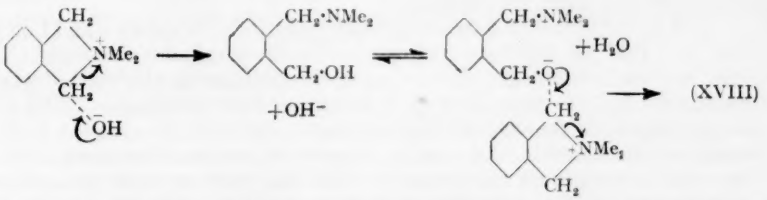
(XVI)

transformed into an unsaturated isomer [possibly 1-2′-dimethylaminoethyl*cyclo*hexene (XIV)] which did not cyclise in acetic acid and which gave 2′-dimethylaminoethyl*cyclo*hexane (X) on catalytic hydrogenation; this interesting reaction will be discussed more fully in a later communication.

Treatment of either *cis*- or *trans*-hexahydrophthalic anhydride with aqueous methylamine gave *cis*-hexahydro-*N*-methylphthalimide (XV). The stereochemical configuration of this imide was shown by (*a*) its formation by distillation of the methylamine salt of *cis*-hexahydrophthalic acid, (*b*) its stability to distillation *in vacuo* at 230°, and (*c*) its hydrolysis by dilute alkali in the cold to *cis*-hexahydrophthalic acid. Analogous reactions of *cis*-hexahydrophthalimide are described by Hückel and Müller (*Ber.*, 1931, **64**, 1981). Reduction of the imide with lithium aluminium hydride gave an octahydro-2-methyl*iso*indole (XVI) which is tentatively formulated as the *cis*-isomer, although further evidence on its stereochemistry is required. Hofmann degradation of the *iso*indole (XVI) gave a low yield of the methine, 1-dimethylaminomethyl-2-methylene*cyclo*hexane (XVII), together with a diamino-ether $C_{20}H_{40}ON_2$. The structure of the methine base (XVII) was proved by (*a*) Emde reduction followed by permanganate oxidation of the 1-methyl-2-methylene*cyclo*hexane to 2-methyl*cyclo*hexanone, (*b*) further Hofmann degradation followed by ozonisation of the 1 : 2-dimethylene*cyclo*hexane, to formaldehyde and *cyclo*hexane-1 : 2-dione, and (*c*) acetic acid cyclisation to the methoacetate of the original *iso*indole (XVI).



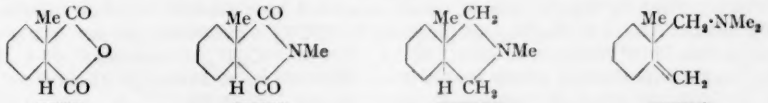
The diamino-ether $C_{20}H_{40}ON_2$ (cf. King, Bovey, Mason, and Whitehead, *J.*, 1953, 250) is tentatively formulated as bis-(2-dimethylaminomethyl*cyclo*hexyl)methyl ether (XVIII), a structure which could readily arise from the *iso*indole methohydroxide by the following series of reactions :



The properties of the diamino-ether are in agreement with the formulation (XVIII). Thus the compound could be neither hydrogenated nor acetylated, but underwent fission with 60% hydrobromic acid to a hydrobromide $C_{10}H_{22}ONBr$, probably 1-dimethylaminomethyl-2-hydroxymethyl*cyclo*hexane hydrobromide (XIX). Hofmann degradation followed by permanganate oxidation also resulted in fission of the ether linkage. The lack of stability of the probable intermediate β-ketonic ether [(XVIII) with :O for each $CH_2{\cdot}NMe_2$ and H] to alkali (derived from the oxidising agent) is understandable (cf. Corbett and Kenner, *J.*, 1953, 2245); the ketone isolated was identified as 2-hydroxymethyl*cyclo*hexanone through the 2 : 4-dinitrophenylhydrazone.

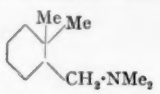
Emde reduction of the above *iso*indole (XVI) gave a 1-dimethylaminomethyl-2-methyl*cyclo*hexane (XX), the constitution of which was shown by Hofmann decomposition followed by oxidation to 2-methyl*cyclo*hexanone.

Reaction of citraconic anhydride and butadiene at 200° gave *cis*-1 : 2 : 3 : 6-tetrahydro-1-methylphthalic anhydride, from which *cis*-hexahydro-1-methylphthalic anhydride (XXI)

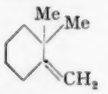


was obtained by catalytic hydrogenation. Treatment of (XXI) with concentrated hydrochloric acid gave the *trans*-acid which was cyclised to the *trans*-anhydride by refluxing acetyl chloride. These configurations are assigned by analogy with those of the corre-

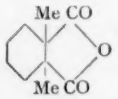
sponding series of compounds lacking the angular methyl group (Diels and Alder, *loc. cit.*). After the completion of this work our attention was drawn to an abstract of a paper by Nazarov and Kucherov (*Chem. Abs.*, 1953, **47**, 5363) who have also prepared the anhydride (XXI) and its *trans*-isomer. Both hexahydromethylphthalic anhydrides gave the same *N*-methylimide, m. p. 52—53°, on treatment with aqueous methylamine; this imide is assigned a *cis*-structure (XXII) by analogy with the structure of the simpler imide described above. Reduction of (XXII) with lithium aluminium hydride gave *cis*(?)-octahydro-2 : 8-dimethyl*iso*indole (XXIII). Hofmann degradation of the *iso*indole (XXIII) gave a methine base $C_{11}H_{21}N$ in low yield, together with a higher-boiling diamino-ether $C_{22}H_{44}ON_2$ which has not been investigated further. The methine may be formulated as 1-dimethylaminomethyl-1-methyl-2-methylene*cyclo*hexane (XXIV) although direct proof of this structure has not been obtained owing to shortage of material. The methine did not undergo further Hofmann decomposition, as would be expected since there is no hydrogen atom available at the β(angular)-position, and treatment with glacial acetic acid gave the original *iso*indole as methoacetate.



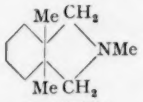
(XXV)



(XXVI)



(XXVII)



(XXVIII)

Emde degradation of the dimethyl*iso*indole (XXIII) resulted in fission of the heterocyclic ring in a different manner from that just described; the product, 2-dimethylaminomethyl-1 : 1-dimethyl*cyclo*hexane (XXV), gave 1 : 1-dimethyl-2-methylene*cyclo*hexane (XXVI) on Hofmann degradation, and this hydrocarbon was oxidised to 2 : 2-dimethyl*cyclo*hexanone with potassium permanganate.

cis-1 : 2 : 3 : 6-Tetrahydro-1 : 2-dimethylphthalic anhydride (Woodward and Loftfield, *J. Amer. Chem. Soc.*, 1941, **63**, 3167) was hydrogenated to the hexahydro-compound (XXVII), and the latter with methylamine gave the *cis*-hexahydrophthalimide which on reduction with lithium aluminium hydride gave *cis*-2 : 8 : 9-trimethyloctahydro*iso*indole (XXVIII). In this series of compounds the *cis*-configuration may confidently be assigned to both the methyl-imide and the *iso*indole, since neither asymmetric carbon atom carries a hydrogen atom. As would be expected the *iso*indole (XXVIII) gave no methine on attempted Hofmann decomposition of its methohydroxide, but instead the original base was recovered in high yield.

Experimental

trans-2-*Allyl*-NN-*dimethyl*cyclo*hexylamine* (III).—*trans*-Decahydroquinoline (Bailey and McElvain, *J. Amer. Chem. Soc.*, 1930, **52**, 4015) was converted into the 1-methyl derivative (Bamberger and Williamson, *Ber.*, 1894, **27**, 1467) by treatment with formaldehyde and formic acid (Clark, Gillespie, and Weisshauss, *ibid.*, 1933, **55**, 4571); the tertiary base yielded a *picrate*, which separated from ethanol in yellow needles, m. p. 171—173° (Found : C, 50·5; H, 5·6; N, 14·6. $C_{16}H_{22}O_7N_4$ requires C, 50·2; H, 5·7; N, 14·7%), and a *methopicrate*, yellow needles (from ethanol), m. p. 141—142° (Found : C, 51·6; H, 6·2; N, 14·4. $C_{17}H_{24}O_7N_4$ requires C, 51·5; H, 6·1; N, 14·1%). Pyrolysis of *trans*-decahydro-1-methylquinoline methohydroxide by Fujise's method (*loc. cit.*) yielded (65%) *trans*-2-allyl-*NN*-dimethyl*cyclo*hexylamine which was separated from a little *trans*-decahydro-1-methylquinoline by fractional crystallisation of the picrates; the methine base picrate (yellow needles from ethanol) had m. p. 100—101° (Fujise gives m. p. 101·5—102°). The unsaturated base was further characterised by the *picrolonate*, which separated from ethanol in yellow needles, m. p. 202—204° (Found: N, 16·2. $C_{21}H_{29}O_5N_5$ requires N, 16·2%), a *methiodide*, prisms (from acetone–ether), m. p. 172—173° (Found: C, 46·8; H, 7·8; I, 41·5. $C_{12}H_{24}NI$ requires C, 46·6; H, 7·8; I, 41·1%), and a *methopicrate*, yellow prisms (from ethanol), m. p. 117—118° (Found : C, 52·8; H, 6·3; N, 13·9. $C_{18}H_{26}O_7N_4$ requires C, 52·7; H, 6·3; N, 13·7%).

Emde Reduction of trans-2-*Allyl*-NN-*dimethyl*cyclo*hexylamine Methochloride*.—*trans*-2-Allyl-*NN*-dimethyl*cyclo*hexylamine methiodide (2 g.) in water (20 c.c.) was shaken with excess of silver chloride for 30 min., and the methochloride solution concentrated and heated on the water-bath with sodium amalgam (5%; 200 g.) which was added in portions during 6 hr.

The resultant allyl*cyclo*hexane (0·3 g.) was purified by distillation from sodium and had b. p. 152—153° (Found: C, 87·1; H, 13·0. Calc. for C_9H_{16}: C, 87·1; H, 12·9%) (de Resseguier, *Bull. Soc. chim.*, 1898, **7**, 431, gives b. p. 148—149°). The hydrocarbon decolorised acidified permanganate. Oxidation of the hydrocarbon (0·45 g.) in acetone (10 c.c.) with potassium permanganate (1·3 g.) at room temperature yielded *cyclo*hexylacetic acid (0·23 g.), b. p. 128—132°/12 mm. (Found: C, 67·3; H, 9·7. Calc. for $C_8H_{14}O_2$: C, 67·6; H, 9·9%), characterised as its amide, m. p. and mixed m. p. 166—168°.

Hofmann Degradation of trans-2-*Allyl*-NN-*dimethyl*cyclo*hexylamine.*—*trans*-2-Allyl-*NN*-dimethyl*cyclo*hexylamine methiodide (2 g.) in ethanol (25 c.c.) and water (25 c.c.) was converted into the methohydroxide which was decomposed by distillation at 200° (bath-temp.). The resultant *hydrocarbon* (0·9 g.), purified by distillation over sodium, had b. p. 148—150° (Found: C, 88·4; H, 11·5. C_9H_{14} requires C, 88·5; H, 11·5%). The hydrocarbon showed no selective absorption in ethanol above 2150 Å.

trans-NN-*Dimethyl*-2-*propyl*cyclo*hexylamine* (IV) *and its Hofmann Degradation.*—trans-2-*Allyl*-NN-*dimethyl*cyclo*hexylamine* (1 g.) in acetic acid (10 c.c.) was hydrogenated at atmospheric pressure in the presence of Raney nickel (H_2 uptake at N.T.P., 112 c.c. Calc. for one double bond, 134 c.c.). Separation of the catalyst, concentration, and basification with ammonia yielded *trans-NN*-dimethyl-2-propyl*cyclo*hexylamine (0·6 g.), b. p. 206—208°. The picrate melted at 114° and the methiodide at 185° (Fujise, *loc. cit.*, gives b. p. 206° and m. p. 114° and 185° respectively). The base was further characterised as a *methopicrate*, yellow needles (from ethanol), m. p. 103—104° (Found: C, 52·6; H, 6·6. $C_{18}H_{28}O_7N_4$ requires C, 52·4; H, 6·8%). The alkaline solution left after ether-extraction of the hydrogenated base (above) was treated with picric acid solution and yielded a mixture of methopicrates (0·4 g.) similar to that described below.

Hofmann degradation of *trans-NN*-dimethyl-2-propyl*cyclo*hexylamine methiodide by Fujise's method (*loc. cit.*) gave 3-propyl*cyclo*hexene (VI), b. p. (over Na) 155°. Fujise gives b. p. 154—155°. The hydrocarbon (0·15 g.) in acetone (10 c.c.) was oxidised with potassium permanganate (0·6 g.) at room temperature and yielded heptane-1 : 4-dicarboxylic acid (0·14 g.), b. p. 150° (bath-temp.)/0·2 mm. [Found: C, 57·3; H, 8·45%; equiv., 95·9; *M* (Rast), 186. Calc. for $C_9H_{16}O_4$: C, 57·4; H, 8·5%; equiv., 94·0; *M*, 188]; the acid was not obtained crystalline (Mellor, *J.*, 1901, **130**, gives m. p. 55°).

Cyclisation of trans-2-*Allyl*-NN-*dimethyl*cyclo*hexylamine* (III) *in Acetic Acid.*—The unsaturated base (1 g.) in glacial acetic acid (10 c.c.) was refluxed for 3 hr., the solution was evaporated under reduced pressure, and the residue basified with ammonia. Extraction with ether yielded no basic fraction, but treatment with excess of aqueous potassium iodide and extraction with chloroform overnight gave a mixture of isomeric methiodides which separated from acetone–ether in colourless prisms, m. p. 223—225° (Found: C, 44·6; H, 7·8; N, 4·75. Calc. for $C_{11}H_{22}NI$: C, 44·7; H, 7·5; N, 4·75%), and was shown by chromatography in chloroform on alumina to contain a little *trans*-decahydro-1-methylquinoline methiodide (corresponding methopicrate, m. p. and mixed m. p. 141—142°). Hofmann degradation of the mixture of methiodides (0·5 g.) yielded *trans*-2-allyl-*NN*-dimethyl*cyclo*hexylamine (III) (0·28 g.). Dehydrogenation of the mixture (0·3 g.) with selenium (0·7 g.) at 320° for 12 hr. and chromatography of the product in light petroleum (b. p. 40—60°) on alumina yielded (*a*) a colourless oil (0·05 g.) which gave no crystalline derivative with picric acid, (*b*) a colourless oil (0·07 g.) which on treatment with alcoholic picric acid afforded 2-methylindole picrate, m. p. 137—138° (Found: C, 50·3; H, 3·6; N, 15·0. Calc. for $C_{15}H_{12}O_7N_4$: C, 50·0; H, 3·3; N, 15·5%) undepressed on admixture with an authentic specimen of m. p. 139°, and (*c*) a colourless oil (0·04 g.) from which was obtained a little quinoline picrate, m. p. and mixed m. p. 202°.

Treatment of the methiodide mixture with aqueous ammonium picrate yielded a mixture of isomeric methopicrates, which could also be obtained directly after cyclisation; the mixture separated from ethanol in yellow needles, m. p. 127—128° (Found: C, 51·6; H, 6·1. Calc. for $C_{17}H_{24}O_7N_4$: C, 51·5; H, 6·1%).

Reactions of cis-2-*Allyl*-NN-*dimethyl*cyclo*hexylamine* (II).—*cis*-Decahydroquinoline was converted into the 1-methyl derivative with formaldehyde and formic acid, and the product characterised as the *picrate*, m. p. 198—199° (Found: C, 50·5; H, 5·8; N, 14·6. $C_{16}H_{22}O_7N_4$ requires C, 50·2; H, 5·7; N, 14·7%), and as the *methopicrate*, m. p. 180—181° (Found: C, 51·6; H, 5·9; N, 13·8. $C_{17}H_{24}O_7N_4$ requires C, 51·5; H, 6·1; N, 14·1%), both yellow needles from ethanol. Hofmann degradation (Fujise, *loc. cit.*) gave *cis*-2-allyl-*NN*-dimethyl*cyclo*hexylamine; the unsaturated base picrate had m. p. 134° (Fujise records m. p. 135—138°). A small proportion of *cis*-decahydro-1-methylquinoline was recovered as picrate. Hofmann and Emde

degradations of *cis*-2-allyl-*NN*-dimethyl*cyclo*hexylamine yielded the hydrocarbons, C_9H_{14}, b. p. 147—148° (Found : C, 88·4; H, 11·6%), and C_9H_{16}, b. p. 150—152° (Found : C, 87·0; H, 13·0%) respectively, apparently identical with those obtained in the same way from the corresponding unsaturated *trans*-base (see above); the hydrocarbon C_9H_{14} showed no selective absorption in the ultra-violet region, and the hydrocarbon C_9H_{16} was oxidised by permanganate in acetone to *cyclo*hexylacetic acid (amide, m. p. 167—168°).

Cyclisation of *cis*-2-allyl-*NN*-dimethyl*cyclo*hexylamine in boiling glacial acetic acid was complete in 2 hr.; the quaternary product was isolated as *methopicrate* (probably a mixture of isomers), yellow needles (from ethanol), m. p. 208—210° (Found: C, 51·5; H, 6·2. $C_{17}H_{24}O_7N_4$ requires C, 51·5; H, 6·1%)

Hofmann Degradation of cis-*Octahydro*-1-*methylindole* (IX).—*cis*-Octahydro-1-methylindole was prepared by the method of Baltrop, King, and Walley (*loc. cit.*). The picrate separated from ethanol as yellow needles, m. p. 200—201° (Found : C, 48·7; H, 5·5; N, 15·4. Calc. for $C_{15}H_{20}O_7N_4$: C, 48·9; H, 5·4; N, 15·2%). King, Bovey, Mason, and Whitehead (*loc. cit.*) give m. p. 204°. Hofmann degradation (Barltrop, King, and Walley, *loc. cit.*) gave 3-2′-dimethylaminoethyl*cyclo*hexene (XI) of which a *picrate*, yellow needles (from ethanol), m. p. 125—126° (Found : C, 49·8; H, 5·5; N, 14·8. $C_{16}H_{22}O_7N_4$ requires C, 50·2; H, 5·7; N, 14·7%), and a *methopicrate*, yellow needles (from ethanol), m. p. 115° (Found : C, 51·3; H, 6·0. $C_{17}H_{24}O_7N_4$ requires C, 51·5; H, 6·1%), were prepared. The methiodide had m. p. 225° (Baltrop, King, and Walley, *loc. cit.*, give m. p. 226°). Catalytic hydrogenation gave 2′-dimethylaminoethyl*cyclo*hexane (X) (methiodide, m. p. 224°; Baltrop, King, and Walley, *loc. cit.*, give m. p. 224°). The *methopicrate*, yellow needles (from ethanol), of (X) had m. p. 114° (Found : C, 51·2; H, 6·4; N, 14·0. $C_{17}H_{26}O_7N_4$ requires C, 51·3; H, 6·5; N, 14·1%). Decomposition of the 2′-dimethylaminoethyl*cyclo*hexane methohydroxide at 200° (bath-temp.) gave *vinyl*cyclo*hexane*, b. p. 150° (bath-temp.) (Found : C, 87·1; H, 12·7. C_8H_{14} requires C, 87·3; H, 12·7%), the constitution of which was shown by oxidation by permanganate in acetone to hexahydrobenzoic acid (amide, m. p. 185—186°).

Hofmann Degradation of 3-2′-*Dimethylaminoethyl*cyclo*hexene* (XI).—Decomposition of the methohydroxide derived from 3-2′-dimethylaminoethyl*cyclo*hexene methiodide (2 g.) in the usual way yielded a *hydrocarbon* (0·3 g.), b. p. (over Na) 134—136° (Found : C, 88·6; H, 11·1. C_8H_{12} requires C, 88·9; H, 11·1%). Ultra-violet absorption : $\lambda_{max.}$ 2295, 2340 (ε 9000, 8500 respectively). Booker, Evans, and Gillam (*J.*, 1940, 1453) give for 1-vinyl*cyclo*hexene (XII) $\lambda_{max.}$ 2300 (ε 8500).

Emde Reduction of 3-2′-*Dimethylaminoethyl*cyclo*hexene Methochloride*.—A solution of this salt, prepared from the methiodide (1 g.), in water (10 c.c.) was reduced by portion-wise addition of sodium amalgam (5%; 150 g.) during 6 hr. at 100°. The crude 3-*ethyl*cyclo*hexene* (0·15 g.) was purified by distillation from sodium and had b. p. 160° (bath-temp.) (Found : C, 87·3; H, 12·9. C_8H_{14} requires C, 87·3; H, 12·7%). Oxidation of this hydrocarbon (0·15 g.) in acetone (5 c.c.) with potassium permanganate (0·5 g.) at room temperature gave 2-ethyladipic acid (0·15 g.), colourless leaflets, m. p. 47—48°, from water [Found : C, 55·0; H, 8·3%; equiv., 88. Calc. for $C_6H_{12}(CO_2H)_2$: C, 55·4; H, 8·0%; equiv., 87]. Lean and Lees (*J.*, 1897, 1067) give m. p. 48—50°. Oxidation with chromium trioxide in acetic acid gave succinic acid.

Cyclisation of 3-2′-*Dimethylaminoethyl*cyclo*hexene* (XI) *in Acetic Acid*.—The unsaturated amine (0·3 g.) in acetic acid (5 c.c.) was refluxed for 5 hr. After concentration and basification with ammonia, no amines were recovered. Addition of potassium iodide and extraction with chloroform yielded a mixture (0·3 g.) of approx. equal parts of *cis*- and *trans*-octahydro-1-methylindole methiodide which were separated by chromatography of a chloroform solution on alumina. The salts were identified by conversion into methopicrates. The *cis*-methopicrate had m. p. 194°, undepressed on admixture with *cis*-octahydro-1-methylindole methopicrate (m. p. 194°) described above; the *trans*-methopicrate had m. p. 169—171° (Found : C, 50·5; H, 6·0. Calc. for $C_{16}H_{22}O_7N_4$: C, 50·2; H, 5·75%), undepressed on admixture with an authentic specimen, m. p. 172°, kindly supplied by Prof. F. E. King.

Reaction of 3-2′-*Dimethylaminoethyl*cyclo*hexene with Alkaline Ethylene Glycol*.—The unsaturated amine (0·5 g.) and potassium hydroxide (5 g.) were heated in ethylene glycol (25 c.c.) containing sufficient water to maintain the temperature of the boiling solution at 150°. After 6 hours' refluxing very little quaternary salt could be isolated, but an unsaturated *base* (0·3 g.), (possibly XIV), b. p. 191°, was obtained. The *picrate*, yellow needles from ethanol, had m. p. 126° (Found : C, 50·1; H, 5·6; N, 14·9. $C_{16}H_{22}O_7N_4$ requires C, 50·2; H, 5·75; N, 14·7%). The *methiodide*, colourless prisms from acetone–ether, had m. p. 234—235° (Found : C, 44·5; H, 7·5; N, 5·0. $C_{11}H_{22}NI$ requires C, 44·7; H, 7·5; N, 4·75%). The base was unaffected by

refluxing acetic acid, but catalytic hydrogenation yielded 2′-dimethylaminoethyl*cyclo*hexane (X), characterised as the picrate, m. p. 150°, and as the methiodide, m. p. 220—221°, undepressed on admixture with authentic specimens prepared as described above.

cis(?)-*Octahydro*-2-*methyliso*indole (XVI).—*cis*- or *trans*-Hexahydrophthalic anhydride (Diels and Alder, *Annalen*, 1928, **460**, 98) (1 g.) was warmed on the water-bath for 15 min. with aqueous methylamine (40%; 1·5 c.c.), the solution evaporated under reduced pressure, and the residue distilled, yielding cis-*hexahydro*-N-*methylphthalimide* (XV), b. p. 140—142°/13 mm.; the imide separated from methanol in colourless prisms, m. p. 47—48° (Found: C, 64·6; H, 7·8. $C_9H_{13}O_2N$ requires C, 64·7; H, 7·8%). Hydrolysis of the imide (0·2 g.) in water (1 c.c.) with sodium hydroxide (0·3 g.) was allowed to proceed for 7 days at room temperature; the resultant *cis*-hexahydrophthalic acid separated from light petroleum (b. p. 40—60°) in colourless prisms, m. p. 192° undepressed on admixture with an authentic specimen (Diels and Alder, *loc. cit.*). The imide (5 g.) in dry ether (500 c.c.) was reduced with lithium aluminium hydride (3·2 g.) (Soxhlet method; Uffer and Schlitter, *Helv. Chim. Acta*, 1948, **31**, 1397). The resultant cis(?)-*octahydro*-2-*methyliso*indole (XVI) had b. p. 70—72°/14 mm., 183—184°/757 mm. (Found: C, 77·6; H, 11·8; N, 10·15. $C_9H_{17}N$ requires C, 77·7; H, 12·2; N, 10·1%). The *picrate*, yellow needles from ethanol, had m. p. 220—222° (decomp.) (Found: C, 49·5; H, 5·7; N, 15·1. $C_{15}H_{20}O_7N_4$ requires C, 49·0; H, 5·4; N, 15·2%). The *picrolonate*, yellow needles from ethanol, had m. p. 171—172° (Found: C, 56·3; H, 5·9; N, 17·1. $C_{19}H_{25}O_5N_5$ requires C, 56·6; H, 6·1; N, 17·4%). The *methiodide* separated from acetone–ether in colourless prisms, m. p. 229—230° (Found: C, 42·7; H, 7·0; N, 4·6. $C_{10}H_{20}NI$ requires C, 42·7; H, 7·1; N, 4·9%). The *methopicrate*, yellow leaflets from ethanol, had m. p. 160—161° (Found: C, 50·0; H, 5·9; N, 14·3. $C_{16}H_{22}O_7N_4$ requires C, 50·2; H, 5·75; N, 14·7%).

Hofmann Decomposition of cis(?)-*Octahydro*-2-*methyliso*indole.—The *iso*indole methiodide (10 g.) was converted into the quaternary hydroxide which was decomposed by distillation *in vacuo*; the product was then redistilled, yielding fractions: (*a*) a colourless oil (2·1 g.), b. p. 60—65°/11 mm., essentially the original octahydro-2-methyl*iso*indole as shown by conversion into the picrate, m. p. 222°, and by failure to cyclise with glacial acetic acid; (*b*) a colourless oil (1·1 g.), b. p. 80—85°/11 mm., a mixture of the *iso*indole and 1-dimethylaminomethyl-2-methylene*cyclo*hexane (XVII); and (*c*) a viscous yellow oil (0·6 g.), b. p. 190—220°/0·4 mm., essentially the diamino-ether, $C_{20}H_{40}ON_2$ (XVIII), described below. Treatment of fraction (*b*) with alcoholic picric acid yielded a little of the *iso*indole picrate, m. p. 222°. The residual 1-dimethylaminomethyl-2-methylene*cyclo*hexane (XVII), b. p. 200°, yielded a *methiodide*, colourless prisms (from acetone–ether), m. p. 142—143° (Found: C, 44·7; H, 7·6; N, 4·4. $C_{11}H_{22}NI$ requires C, 44·8; H, 7·5; N, 4·75%). When this salt (0·5 g.) was converted into the methohydroxide in the usual way and the latter distilled the products were: (*a*) recovered methine base (0·1 g.), identified as the methiodide, m. p. 142—143°; (*b*) 1 : 2-dimethylene*cyclo*hexane (0·1 g.), b. p. 155° (bath-temp.), $\lambda_{max.}$ (in EtOH), 2300 Å (ε 14,130). Ozonisation of the unsaturated hydrocarbon (0·1 g.) in carbon tetrachloride (5 c.c.) at room temperature, followed by steam-distillation of the solution, gave formaldehyde (25%, estimated colorimetrically) and *cyclo*hexane-1 : 2-dione, identified as the bisphenylhydrazone, m. p. 151° (Found: C, 74·1; H, 6·6; N, 19·0. Calc. for $C_{18}H_{20}N_4$: C, 73·9; H, 6·8; N, 19·3%). Kötz, Blendermann, Rosenbusch, and Sirringhaus (*Annalen*, 1913, **400**, 67) give m. p. 150—151°.

Emde Reduction of 1-*Dimethylaminomethyl*-2-*methylene*cyclo*hexane*.—(a) *With sodium amalgam.* An aqueous solution of the methochloride of the foregoing base, derived from methiodide (0·5 g.) and silver chloride, was reduced with sodium amalgam (150 g.; 5%) which was added portion-wise during 6 hr. The products were methine base (0·15 g.; methiodide, m. p. 142—143°) and 1-*methyl*-2-*methylene*cyclo*hexane* (0·1 g.), b. p. 145° (bath-temp.) (Found: C, 87·2; H, 12·5. C_8H_{14} requires C, 87·3; H, 12·7%).

(b) *With sodium in liquid ammonia.* The methine methiodide (0·5 g.) in liquid ammonia (150 c.c.) was treated with sodium, added in small portions until a permanent blue colour remained. The hydrocarbon (0·08 g.) isolated from the reaction mixture was identical with that obtained above.

Oxidation of 1-*Methyl*-2-*methylene*cyclo*hexane*.—The hydrocarbon (0·1 g.) in acetone (10 c.c.) was oxidised at room temperature with potassium permanganate (0·6 g.) which was added portion-wise during 2 hr. No acidic product was obtained, but a ketone (0·08 g.) was isolated and identified as 2-methyl*cyclo*hexanone through the 2 : 4-dinitrophenylhydrazone, m. p. 133°, and the semicarbazone, m. p. 193°, undepressed on admixture with authentic specimens.

Action of Glacial Acetic Acid on 1-*Dimethylaminomethyl*-2-*methylene*cyclo*hexane*.—The base (0·3 g.) in acetic acid (10 c.c.) was refluxed for 3 hr. After evaporation and basification with

ammonia, no base remained. Addition of ammonium picrate to a portion of the alkaline solution yielded a methopicrate (0·45 g.), m. p. 160—161° (after crystallisation from ethanol) undepressed on admixture with the octahydro-2-methyl*iso*indole methopicrate of the same m. p. (described above). Addition of potassium iodide to the remainder of the above alkaline solution and extraction with chloroform overnight gave a methiodide, m. p. 230°, not depressed on admixture with methiodide, m. p. 229—230°, derived from the *iso*indole.

Reactions of the Diamino-ether (XVIII), $C_{20}H_{40}ON_2$.—The *ether* [fraction (*c*), p. 973] [Found : C, 73·9; H, 12·6; N, 8·6%; *M* (in *cyclo*hexane), 317. $C_{20}H_{40}ON_2$ requires C, 74·0; H, 12·4; N, 8·6%; *M*, 324] was characterised as the *dipicrate*, yellow prisms (from ethanol), m. p. 168° (Found : C, 49·4; H, 5·8; N, 14·4. $C_{32}H_{46}O_{15}N_8$ requires C, 49·1; H, 5·9; N, 14·3%), the *dimethiodide*, colourless prisms (from acetone–ether), m. p. 176—178° (Found : C, 43·1; H, 7·5; N, 4·9. $C_{22}H_{46}ON_2I_2$ requires C, 43·4; H, 7·6; N, 4·6%), and the *dimethopicrate*, yellow prisms (from ethanol), m. p. 116—117° (Found: C, 50·2; H, 6·1; N, 13·6. $C_{34}H_{50}O_{15}N_8$ requires C, 50·4; H, 6·2; N, 13·8%). The ether was not hydrogenated in the presence of Raney nickel at pressures up to 5 atm., and did not react with acetic anhydride. Treatment with boiling concentrated hydrobromic acid for 1 hr. gave 1-dimethylaminomethyl-2-hydroxymethyl*cyclo*hexane hydrobromide (XIX), which separated from acetone in colourless needles, m. p. 233—234° (Found : C, 48·0; H, 8·4. $C_{10}H_{21}ON,HBr$ requires C, 47·7; H, 8·7%). Hofmann degradation of the diamino-ether methiodide (0·8 g.) yielded the diamino-ether (0·1 g.) and an unsaturated nitrogen-free ether (XVIII; with $=O$ for H and $CH_2{\cdot}NMe_2$), b. p. 180° (bath-temp.). Oxidation of the unsaturated ether with potassium permanganate in acetone at room temperature gave 2-hydroxymethyl*cyclo*hexanone (Mannich and Brose, *Ber.*, 1923, **56**, 833), characterised as the 2 : 4-*dinitrophenylhydrazone*, red prisms (from ethanol), m. p. and mixed m. p. 125—126° (Found : C, 50·2; H, 5·4. $C_{13}H_{16}O_5N_4$ requires C, 50·6; H, 5·2%).

Emde Reduction of the Octahydro-2-methylisoindole.—Reduction of a refluxing methochloride solution prepared from the *iso*indole methiodide (2 g.) with sodium amalgam (200 g., 5%), added during 6 hr., gave 1-dimethylaminomethyl-2-methyl*cyclo*hexane (XX) (0·15 g.), characterised as the *picrate*, yellow needles (from ethanol), m. p. 200—201·5° (Found : C, 50·6; H, 6·4. $C_{16}H_{24}O_7N_4$ requires C, 50·0; H, 6·3%), the *methiodide*, colourless prisms (from acetone–ether), m. p. 198—201° (Found : C, 44·25; H, 8·0. $C_{11}H_{24}NI$ requires C, 44·4; H, 8·1%), and the *methopicrate*, yellow plates (from ethanol), m. p. 156—158° (Found : C, 51·1; H, 6·1. $C_{17}H_{26}O_7N_4$ requires C, 51·3; H, 6·5%).

Hofmann Degradation of 1-*Dimethylaminomethyl-2-methyl*cyclo*hexane* (XX).—The base methiodide (0·8 g.) was converted into an aqueous solution of the methohydroxide in the usual way. Evaporation of the solution and distillation of the residue at 150° gave an unsaturated product (0·15 g.) which was oxidised in acetone (10 c.c.) with potassium permanganate (0·6 g.) added during 2 hr. There was thus obtained 2-methyl*cyclo*hexanone (0·09 g.), characterised as its 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 132—133°.

Preparation of cis- *and* trans-*Hexahydro-1-methylphthalic Anhydride.*—After citraconic anhydride (10 g.) and butadiene (6 g.) had been heated in dry benzene (15 c.c.) at 210° for 72 hr., the cooled mixture was added to sodium hydroxide (10%; 80 c.c.) and freed from benzene on the water-bath. Polymeric materials were separated by filtration and the filtrate acidified with hydrochloric acid and extracted with ether for 48 hr. The residue from the ether was slowly distilled *in vacuo*, yielding *cis*-1 : 2 : 3 : 6-tetrahydro-1-methylphthalic anhydride, b. p. 138—140°/13 mm. (Found : C, 65·2; H, 5·8. Calc. for $C_9H_{10}O_3$: C, 65·1; H, 6·1%). Hydrogenation of this anhydride (0·9 g.) in ethanol (5 c.c.) in the presence of Raney nickel was complete in 20 min. (H_2 uptake at N.T.P., 110 c.c. Calc. for one double bond, 121·5 c.c.). The resulting *cis*-hexahydro-1-methylphthalic anhydride (XXI) (0·8 g.) was distilled at 136°/13 mm., and crystallised from methanol in colourless prisms, m. p. 70—71 (Found : C, 64·1; H, 7·0. Calc. for $C_9H_{12}O_3$: C, 64·3; H, 7·1%) (Nazarov and Kucherov, *loc. cit.*, give m. p. 71—72°). This anhydride (1 g.), when heated with concentrated hydrochloric acid (5 c.c.) at 120° for 3 hr., yielded *trans*-hexahydro-1-methylphthalic acid, colourless prisms (from benzene), m. p. 211—212° (Nazarov and Kucherov, *loc. cit.*, give m. p. 212—213°). The acid (1·5 g.) was refluxed for 24 hr. with acetyl chloride (10 c.c.), and the product distilled at 138—140°/14 mm., giving *trans*-hexahydro-1-methylphthalic anhydride (0·6 g.), colourless prisms, m. p. 86—87°, from light petroleum (b. p. 60—80°) (Found : C, 64·4; H, 7·2. Calc. for $C_9H_{12}O_3$: C, 64·3; H, 7·1%) (Nazarov and Kucherov, *loc. cit.*, give m. p. 87—88°).

cis(?)-*Octahydro-2 : 8-dimethylisoindole* (XXIII).—The above *cis*-anhydride (0·9 g.) was warmed with aqueous methylamine (40%; 3 c.c.) on the water-bath for 20 min., the reaction mixture evaporated, and the residue distilled *in vacuo*, giving the *N*-methylimide (XXII) of

cis-hexahydro-1-methylphthalic acid, b. p. 137—139°/13 mm., which crystallised from methanol in colourless prisms, m. p. 52—53° (Found: C, 66·0; H, 8·0; N, 7·2. $C_{10}H_{15}O_2N$ requires C, 66·3; H, 8·3; N, 7·7%). Reduction of this imide (1 g.) in ether (250 c.c.) with lithium aluminium hydride (1 g.) gave the iso*indole* (XXIII) (0·8 g.), b. p. 168—170° (Found: C, 78·2; H, 12·3; N, 9·2. $C_{10}H_{19}N$ requires C, 78·4; H, 12·4; N, 9·15%). The base yielded a *picrate*, yellow needles (from ethanol), m. p. 226—227° (Found: C, 50·6; H, 5·7; N, 14·7. $C_{16}H_{22}O_7N_4$ requires C, 50·2; H, 5·7; N, 14·7%), a *methiodide*, colourless leaflets (from acetone–ether), m. p. 236—237° (Found: C, 44·5; H, 7·3; N, 4·6. $C_{11}H_{22}NI$ requires C, 44·8; H, 7·5; N, 4·75%), and a *methopicrate*, yellow prisms (from ethanol), m. p. 203—204° (Found: C, 51·6; H, 6·0; N, 13·9. $C_{17}H_{24}O_7N_4$ requires C, 51·5; H, 6·1; N, 14·1%).

Hofmann Degradation of cis(?)-*Octahydro*-2 : 8-*dimethyl*iso*indole*.—The *iso*indole methiodide (7 g.) was converted into quaternary hydroxide which was decomposed in the usual manner. Redistillation of the oily product gave (*a*) a colourless oil (1·8 g.), b. p. 75—94°/11 mm., and (*b*) a viscous yellow oil (0·3 g.), b. p. 180—200°/11 mm. Fraction (*a*) on treatment with methanolic picric acid gave a good yield of the picrate of the original *iso*indole (XXIII); decomposition of the picrate mother-liquors with alkali yielded an unsaturated base, probably 1-dimethylaminomethyl-1-methyl-2-methylene*cyclo*hexane (XXIV) (0·25 g.) from which was obtained a *methiodide*, colourless prisms (from acetone–ether), m. p. 202—203° (Found: C, 46·2; H, 7·4; N, 4·75. $C_{12}H_{24}NI$ requires C, 46·6; H, 7·8; N, 4·5%), and a *methopicrate*, yellow prisms (from ethanol), m. p. 159—160° (Found: C, 52·0; H, 6·4; N, 13·5. $C_{18}H_{26}O_7N_4$ requires C, 52·7; H, 6·3; N, 13·6%). Attempted Hofmann decomposition of the methiodide, m. p. 202—203°, gave no hydrocarbon, but an oily base was obtained which yielded the original methiodide on treatment with methyl iodide.

When the unsaturated base [(XXIV) from fraction (*a*) above] was refluxed with acetic acid, and the cyclised product isolated as methopicrate, yellow prisms of m. p. 204° were obtained, undepressed on admixture with the methopicrate of the above octahydro-2 : 8-dimethyl*iso*indole (XXIII) of the same m. p.

Treatment of fraction (*b*) (above) with methanolic picric acid gave a *picrate* which recrystallised from ethanol in yellow prisms, m. p. 156° (Found: C, 50·2; H, 6·1. $C_{34}H_{50}O_{15}N_8$ requires C, 50·4; H, 6·2%).

Emde Degradation of cis(?)-*Octahydro*-2 : 8-*dimethyl*iso*indole*.—The *iso*indole methiodide (0·8 g.) in liquid ammonia (200 c.c.) was treated with a slight excess of sodium, and the resulting basic mixture (0·35 g.) separated by fractional crystallisation of the picrates from ethanol. There was thus obtained octahydro-2 : 8-dimethyl*iso*indole picrate, yellow needles, m. p. and mixed m. p. 226—227° (Found: C, 50·3; H, 5·5; N, 14·7. $C_{16}H_{22}O_7N_4$ requires C, 50·2; H, 5·75; N, 14·7%), and a larger fraction, yellow prisms, m. p. 136—137° (Found: C, 51·5; H, 6·0; N, 14·1. $C_{17}H_{26}O_7N_4$ requires C, 51·3; H, 6·5; N, 14·1%). The latter *picrate* is that of 2-dimethylaminoethyl-1 : 1-dimethyl*cyclo*hexane (XXV); the corresponding *methiodide* separated from acetone–ether in colourless prisms, m. p. 267—268° (Found: C, 46·4; H, 8·0; N, 4·2. $C_{12}H_{26}NI$ requires C, 46·3; H, 8·4; N, 4·5%), and the *methopicrate*, yellow leaflets from ethanol, had m. p. 169—170° (Found: C, 51·8; H, 6·8. $C_{18}H_{28}O_7N_4$ requires C, 52·4; H, 6·8%).

Hofmann Degradation of the Methiodide of the Base (XXV).—The methiodide (0·4 g.) was converted into methohydroxide, distillation of which gave a basic fraction (0·12 g.) and 1 : 1-dimethyl-2-methylene*cyclo*hexane (XXVI) (0·15 g.), b. p. 155°. Oxidation of the hydrocarbon (0·15 g.) in acetone (10 c.c.) with potassium permanganate (0·6 g.) at room temperature gave 2 : 2-dimethyl*cyclo*hexanone (0·09 g.), identified as the semicarbazone, m. p. 200°, undepressed on admixture with an authentic specimen (Auwers and Lange, *Annalen*, 1913, **401**, 320).

cis-*Octahydro*-2 : 8 : 9-*trimethyl*iso*indole* (XXVIII).—Catalytic hydrogenation of *cis*-1 : 2 : 3 : 6-tetrahydro-1 : 2-dimethylphthalic anhydride (Woodward, *loc. cit.*) over Raney nickel in ethanol at atmospheric pressure yielded *cis*-hexahydro-1 : 2-dimethylphthalic anhydride (XXVII), b. p. 139—140°/12 mm., which recrystallised from benzene in colourless prisms, m. p. 56° (Found: C, 65·7; H, 7·6. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·7%). This anhydride (0·9 g.), when warmed on the water-bath for 15 min. with aqueous methylamine (40%; 3 c.c.), yielded the *cis*-*N*-methylimide (0·8 g.), b. p. 141°/12 mm. Reduction of the imide (0·8 g.) in ether (250 c.c.) with lithium aluminium hydride (1·5 g.) gave *cis*-octahydro-2 : 8 : 9-trimethyl*iso*indole (XXVIII) (0·5 g.), b. p. 186°, characterised as the *picrate*, yellow needles (from ethanol), m. p. 227—230° (Found: C, 51·6; H, 6·0; N, 14·4. $C_{17}H_{24}O_7N_4$ requires C, 51·5; H, 6·1; H, 14·1%), the *picrolonate*, yellow prisms (from ethanol), m. p. 188—189° (Found: N, 16·3. $C_{21}H_{29}O_8N_5$ requires N, 16·2%), the *methopicrate*, yellow prisms (from ethanol), m. p. 240—241° (Found: C, 52·7; H, 6·2; N, 13·5.

$C_{18}H_{26}O_7N_4$ requires C, 52·7; H, 6·3; N, 13·7%), and the *methiodide*, colourless hygroscopic prisms (from acetone–ether), m. p. 231° (Found: C, 46·8; H, 7·8; N, 4·5. $C_{12}H_{24}NI$ requires C, 46·6; H, 7·8; N, 4·5%). The methiodide gave no methine on attempted Hofmann decomposition, the *iso*indole (XXVIII) being recovered.

We thank the Department of Scientific and Industrial Research for a maintenance grant (to B. B.), and Imperial Chemical Industries Limited for partly defraying the expenses of this work.

THE UNIVERSITY, SHEFFIELD, 10. [*Received, October 24th,* 1953.]

The Quenching of the Fluorescence of Anthracene. The Transition from Strong to Weak Quenching.

By H. W. MELHUISH and W. S. METCALF.

[Reprint Order No. 4788.]

Quenching of fluorescence in solution occurs when quencher molecules and excited molecules occupy contiguous positions in a liquid. Strong quenchers are limited by the viscosity-controlled rate of formation of neighbouring pairs, while weak quenchers are limited by the concentration of such pairs and the efficiency of collisions within them. An equation is derived from this model which describes the observed behaviour of quenchers of intermediate strength. A photometer is described which is suitable for the precise measurement of relative fluorescence intensities.

A MECHANISM which describes the quenching of the fluorescence of solutions of anthracene by substances which deactivate the excited molecules on every encounter has been given by Bowen and Metcalf (*Proc. Roy. Soc.*, 1951, *A*, **206**, 437). This scheme may now be extended to cases where encounters are less effective.

As before, quenching is considered to occur only in collisions between nearest neighbours. In the present extension there is included the possibility of an excited molecule and a quencher molecule vacating contiguous positions before quenching occurs. Let α be the fraction of anthracene in encounters. The relevant processes and their rates are

		Rates, etc.
Absorption	$A + h\nu \longrightarrow A^*$	$(1-\alpha)I_{abs.}$
	$AQ + h\nu \longrightarrow A^*Q$	$\alpha I_{abs.}$
Fluorescence	$A^* \longrightarrow A + h\nu'$	$k_f[A^*]$
	$A^*Q \longrightarrow AQ + h\nu'$	$k_f[A^*Q]$
Quenching	$A^*Q \longrightarrow$ Products or energy degradation	$k_3[A^*Q]$
Encounter equilibria	$A + Q \underset{k_2}{\overset{k_1}{\rightleftharpoons}} AQ$	$[AQ] = K[A][Q]$
	$A^* + Q \underset{k_2}{\overset{k_1}{\rightleftharpoons}} A^*Q$	$K = k_1/k_2$

A and Q represent anthracene and quenching substance, respectively.

It is assumed that excitation does not appreciably alter the rate constants for formation and dissociation of encounters, and encounter formation does not sensibly alter the rate constant k_f for fluorescence emission.

Putting $d[A^*]/dt = d[A^*Q]/dt = 0$ and noting that $(1-\alpha) = 1/(1+K[Q])$, we have

$$\frac{f_0}{f} = \frac{k_2' + (1+k_3')(1+k_1'[Q])}{k_2' + (1+k_1'[Q]) + k_3'/(1+K[Q])} \quad . \quad . \quad . \quad . \quad . \quad (1)$$

A prime denotes division by k_f; f and f_0 are respectively the fluorescence intensities with and without quencher added.

This expression applies only to dilute solutions, since no account is taken of the existence of encounters containing more than one quencher molecule.

k_f is of the order 10^8 and is presumed to be independent of the composition of the

paraffin mixtures used as solvents. Units of time are taken as seconds, and of concentration as moles/l.

K, the equilibrium constant for the formation of encounters, is of the order of unity if the molecules are equal-sized spheres randomly arranged on a close-packed hexagonal lattice. For real solutions, no large change is expected if excited and quencher molecules show no strong preferential interaction. Since $K = k_1/k_2$, k_1 and k_2 are of the same order and depend similarly on the mean diffusion coefficient D of the interacting species. They are approximately $10^{15}D$, which for common organic solvents ($\eta \sim 0{\cdot}01$ poise) is about 10^{10} (*idem, loc. cit.*; $k_1 = k_e$); k_1 and k_2 are not expected to differ greatly for various quenchers, because diffusion coefficients are not sensitive to small changes in the size of molecules.

Equation (1) may be further reduced for comparison with experimental values of the quenching constant k defined by $k = (f_0/f - 1)/[Q]$. As $[Q]$ approaches zero, k approaches k_0, given by

$$k_0 = k_3'(k_1' + K)/(1 + k_2' + k_3') \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The application of this equation to a number of quenchers of the fluorescence of anthracene is shown in Fig. 1, *a* and *b*, Fig. 1*b* being an enlargement of that part of Fig. 1*a*

FIG. 1*a*.

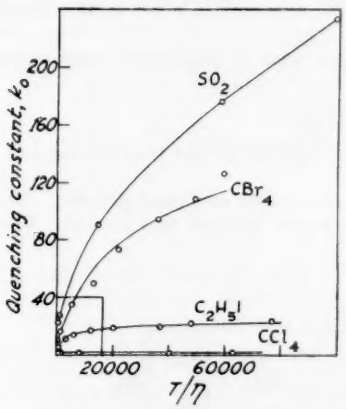
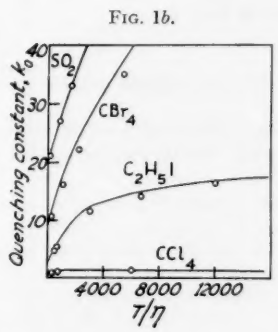


FIG. 1*b*.



shown at the bottom left-hand corner. The points are experimental. The curves are calculated from equation (2), the following values of K and k_3' being used:

	SO_2	CBr_4	C_2H_5I	CCl_4		SO_2	CBr_4	C_2H_5I	CCl_4
K	20	9	3·2	2·5	k_3'	>500	40	7·5	0·44

k_1' is as found for SO_2 at each fluidity (*idem, loc. cit.*) and the same value is used for the other quenchers. The deviations from the predicted values are not greater than can be attributed to this approximation.

For *weak* quenchers such as carbon tetrachloride in light petroleum, the dissociation of encounters is much more probable than the quenching process: $k_2 \gg k_3$. Equation (2) becomes

$$k_0 = k_3'K \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

which contains no terms dependent on the viscosity. As the viscosity is increased by the addition of medicinal paraffin to the solvent, the rates of formation and dissociation of encounters are reduced until k_2 is no longer much larger than k_3. Quenching then becomes dependent on viscosity and at infinite viscosity ($k_1 = k_2 = 0$), the quenching constant falls to

$$k_0 = k_3'K/(1 + k_3') \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

k_3' and K may thus be calculated from the experimental values of k_0 in mixed paraffin solvents. The product $k_3'K$ is obtainable with accuracy from the horizontal part of the

curve, but the nature of the equations (3) and (4) and the extrapolation to infinite viscosity allow considerable latitude in the separate values of k_3' and K.

For *strong* quenchers of the fluorescence of anthracene such as oxygen or sulphur dioxide, quenching is more probable than the dissociation of encounters at all accessible viscosities: $k_3 \gg k_2$. Hence

$$k_0 = (k_1' + K)k_3'/(1 + k_3')$$

At infinite viscosity ($k_1' = 0$)

$$k_0 = Kk_3'/(1 + k_3')$$

If, as is usual in these cases, $k_3' \gg 1$, the term $k_3'/(1 + k_3')$ may be omitted. If the equation is extended to substances other than anthracene this last condition may not always apply.

When $[Q] = 0$, equation (1) reduces to

$$k = k_1' + K + k_1'K[Q]$$

for strong quenchers of anthracene fluorescence ($k_3' \gg 1$ and $k_3 \gg k_2$). This equation has been shown to describe the effect of quencher concentration on the quenching of anthracene fluorescence by carbon tetrabromide (*idem, loc. cit.*) although it is not certain that $k_3 \gg k_2$ in the less viscous solvents.

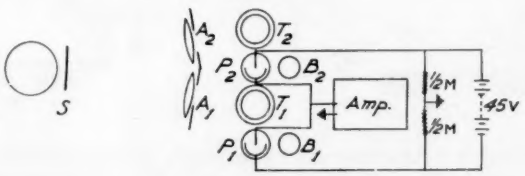
Ethyl iodide is a quencher of *intermediate* type, and its conformity with equation (2) is shown in Fig. 1.

Experimental

The data for sulphur dioxide and carbon tetrabromide at 20° are from Bowen and Metcalf (*loc. cit.*).

The solvents used were mixtures of light petroleum and medicinal paraffin. They were shaken with fuming sulphuric acid until no more brown material was formed. Fluorescent

Fig. 2.



material remaining was removed by a silica-gel column, without a preliminary washing with water which gives troublesome emulsions. The other materials were colourless. Fractional distillation (10 theoretical plates) of the reagent-grade materials gave middle fractions whose quenching power did not differ from that of the combined fractions.

The solutions were freed from oxygen by boiling under reflux, and entered the photometer without contact with air. They could be returned for further boiling if necessary. The concentration of anthracene was that at which maximum fluorescence reached the photo-cell, namely, 0·056 g./l. The quenching coefficient $k = (f_0/f - 1)/[Q]$, measured at 18° and over a range of low concentrations of carbon tetrachloride and ethyl iodide, was extrapolated to $[Q] = 0$.

The photometer used is shown in Fig. 2. Solutions whose relative intensities are required are placed in turn in the temperature-controlled tube T_1, and the aperture A_1 is adjusted till the fluorescence intensity matches that of a reference solution in a similar tube T_2. The apertures A_1 are then inversely as the fluorescence intensities at constant illumination.

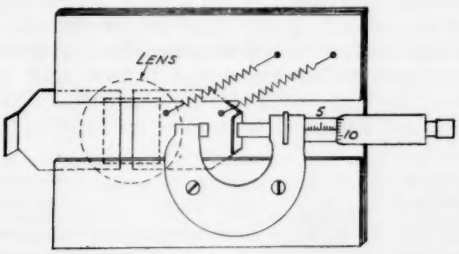
Matching is achieved when the potential at the junction of the photocells P_1 and P_2 (Philips 90 AV) connected in series is at earth potential and does not change when the shutter S is opened, as shown by the D.C. amplifier. Large changes in the intensity of the source do not affect the aperture required for matching if the dark currents are equal, as can be arranged by passing a small adjustable current through one of the bulbs B_1, B_2 near the photo-cells. This adjustment is important because the dark current is frequently larger than the photo-current.

Movement of the arc in the 80 w high-pressure mercury lamp used as source is a serious and frequent cause of irreproducibility. By lateral adjustment of the lenses a position may be found where large movements of the lamp in any direction do not affect the balance. Presumably, the fluorescent images are identically related each to its respective photo-cell, when this adjustment is complete. None of the several other optical arrangements tried permitted such complete compensation of lamp movements.

Fluctuations accompanying arc movements were still noticeable. They were traced to irregularities of the lamp bulb in the respective light paths. By rotation of the lamp a sufficiently uniform portion of the quartz and glass envelopes can usually be found.

The amplifier should be sensitive to about 1 mv, and should be stable to this extent for a few minutes. The input impedance should exceed the dynamic resistance of the photo-cells, which is of the order 10^{10} ohms. Hill's circuit (Dole, "Glass Electrode," Wiley, New York, 1951, p. 58) is satisfactory. An amplifier, based on Nielsen's work (*Rev. Sci. Instr.*, **1947**, **18**, 18), also satisfies these requirements, as does the amplifier described by Elmore and Sands ("Electronics," McGraw-Hill, New York, 1949, p. 190). The photo-cells and the first stage of the amplifier require careful insulation, which is improved by drying with silica gel or treating the glass surfaces with silicone fluid.

FIG. 3.



The aperture is controlled by a micrometer, aperture area being proportional to the scale reading. The sensitivity and stability are more than is required to set the micrometer to 0·01 mm. The maximum aperture is 2·5 cm. An aperture of 0·01 mm. corresponds to a photocurrent of about 2×10^{-12} amp. in the present experiments. The optical equivalence of each portion of the scale is tested and the scale is corrected by noting the aperture in various regions of the scale required to balance a fixed aperture in the other beam. The micrometer aperture is constructed to facilitate this test as shown in Fig. 3. (This design permits all edges whose straightness is essential to be cut with a guillotine.)

The spring fitting slider on the left is pushed in and both sliders advanced across the lens face by the micrometer to any desired position. The micrometer may then be reversed to adjust the aperture to balance. Should there by any lack of optical equivalence for various parts of the lens face, a correction table may be prepared, or a strip of thin metal may be shaped and attached to the upper edge of the aperture to make the scale uniform.

The quality of the optical parts is not important, because the calibration above allows for any imperfections in them. The tubes T_1 and T_2 and their water jackets are of ordinary glass tubing rigidly fixed. Light scattered from the source (3650 Å) was removed from the fluorescence by a filter of anthracene in bromobenzene.

The rate of formation of encounters, their equilibrium concentration, and the frequency and efficiency of collisions between nieghbouring molecules are all relevant to the quenching of fluorescence in solution. In favourable cases, some of these quantities can be separately determined. A study of their variation with pressure, temperature, and, in the case of electrolytes, with dielectric constant and ionic strength, may be expected to yield results of considerable interest.

VICTORIA UNIVERSITY COLLEGE,
WELLINGTON, NEW ZEALAND.

[*Received, November 11th*, 1953.]

The Oxidation of Some Aromatic Amines with Persulphate.

By E. Boyland and Peter Sims.

[Reprint Order No. 4807.]

The action of alkaline persulphate on a number of substituted aromatic amines has been investigated. In all cases *o*-aminophenyl sulphates are found, irrespective of the orienting influence of other functional groups.

The action of alkaline persulphate on a number of simple aromatic amines yields the corresponding *o*-aminophenyl sulphate esters (Boyland, Manson, and Sims, *J.*, 1953, 3623), and its action on substituted aromatic amines has now been investigated. In all cases, substituted *o*-aminophenyl sulphates were obtained, and there was no evidence of the introduction of the sulphate group in any other position.

The esters were usually isolated as their sodium or potassium salts and, in most cases, acidification of aqueous solutions of the salts yielded the crystalline free acids. All the esters described were readily hydrolysed by hot acid to the corresponding aminophenols, so that the positions of the sulphate groups could be determined. In some cases, where the identities of the aminophenols were in doubt, the dibenzoyl derivatives were converted into the corresponding 2-phenylbenzoxazoles (and benzoic acid) by the action of heat, reactions characteristic of the derivatives of *o*-aminophenols. The esters, together with the derived aminophenols and 2-phenylbenzoxazoles, are listed in the Table.

Substituted aniline	Substituted *o*-aminophenyl hydrogen sulphate and *o*-aminophenol	Substituted 2-phenyl-benzoxazole	Substituted aniline	Substituted *o*-aminophenyl hydrogen sulphate and *o*-aminophenol	Substituted 2-phenyl-benzoxazole
2-Methyl	3-Methyl [1]	4-Methyl	4-Phenyl	5-Phenyl	(2 : 6-Diphenyl-benzoxazole)
3-Methyl	4-Methyl	—			
4-Methyl	5-Methyl	6-Methyl	4-Bromo	5-Bromo	6-Bromo
2-Carboxy	3-Carboxy	—	3-Chloro	4-Chloro	—
4-Carboxy	5-Carboxy	—	2-Nitro	3-Nitro [1]	—
4-Sulpho	5-Sulpho [2]	—			

[1] The free sulphuric esters did not separate when aqueous solutions of the potassium salts were acidified (cf. 2-aminophenyl hydrogen sulphate, Burkhardt and Wood, *J.*, 1929, 141).
[2] A monopotassium salt was obtained when an aqueous solution of the disalt was acidified.

Examination of the crude sulphates and their acid-hydrolysis products on paper chromatograms showed that only one major product was usually present. In the oxidations of *m*-toluidine and *m*-chloroaniline, however, second products, present in much smaller amounts than the first, were also detected. Both these amines have unsymmetrical free positions *ortho* to the amino-groups, and it seems probable that isomeric *ortho*-aminophenyl sulphates are formed in these cases, although the products isolated were substituted in the 4-position to the methyl and chloro-group respectively. Examination of the oxidation products of anthranilic acid showed the presence of a small amount of a second ester, which we have been unable to identify; the acid hydrolysis products of the crude sulphate do not contain 5-hydroxyanthranilic acid. The acid hydrolysis products of the crude sulphates derived from aniline and dimethylaniline (cf. Boyland *et al.*, *loc. cit.*) showed the presence of *o*-aminophenol and *o*-dimethylaminophenol respectively, but no *para*-substituted amines could be detected.

The aminophenol derived from the sulphanilic acid oxidation had m. p. >300° and, although Doub, Schaefer, Bambas, and Walker (*J. Amer. Chem. Soc.* 1951, **73**, 903) report that 4-amino-2-hydroxybenzenesulphonic acid (the other possible product from our oxidation) has m. p. 275° (decomp.), a preparation of this acid (Thorpe and Williams, *Biochem. J.*, 1941, **35**, 61) did not melt below 300°. Thorpe and Williams (*loc. cit.*; cf. Miller, Mosher, Gray, and Whitmore, *J. Amer. Chem. Soc.*, 1949, **71**, 3559) prepared pyridinium

4-acetamido-2-acetoxybenzenesulphonate, m. p. 170—171°, from the acid with acetic anhydrine and pyridine, whereas our acid, under similar conditions, yielded a pyridinium salt of m. p. 156—158°. It is concluded, therefore, that our acid is 4-amino-3-hydroxybenzenesulphonic acid.

The oxidations were accompanied by the formation of coloured products, evidently arising from attack on the amino-groups; these have not been investigated in detail. Witt and Kopetschni (*Ber.*, **1912**, **45**, 1134) found that acidified persulphate (catalysed with silver nitrate) oxidised aromatic amines to nitro-compounds.

Under our experimental conditions, persulphate does not yield sulphuric esters with benzoic acid, nitrobenzene, toluene, benzene, or naphthalene. Aniline, 2-naphthylamine, and dimethylaniline readily form sulphuric esters (Boyland *et al.*, *loc. cit.*), but persulphate is without effect on acetanilide and 2-acetamidonaphthalene. Similarly, pyridine and *cyclo*hexylamine do not yield sulphuric esters with this reagent. The reaction differs from Elbs's persulphate oxidation of phenols, where substitution occurs mainly in the *para*-position, and less readily in the *ortho*-position when the *para*-position is blocked. It is hoped that experiments now in hand will provide some evidence of the mechanism involved in our oxidation.

Experimental

In most cases the m. p.s of the free-acid esters depend on the rate of heating. Occasionally, preparations of these acids darkened at temperatures many degrees below the normal m. p., and did not then melt below 300°.

Persulphate Oxidations.—The amine (5 g.), in water (250 ml.), was brought into solution by the addition of acetone, or, in the case of the amines containing an acidic group, by the addition of 2N-sodium or -potassium hydroxide. 2N-Sodium or -potassium hydroxide (20% excess) was added, followed by the theoretical amount of sodium or potassium persulphate, added in aqueous solution during 8 hr. with continuous stirring. The mixture was kept overnight, evaporated to 200 ml. under reduced pressure, and filtered. The solution was washed with ether and treated as indicated below.

Oxidation of the Toluidines.—The solution obtained as described above was extracted with butanol (6 × 150 ml.), the butanol extract was dried (Na_2SO_4), and a slight excess of 2N-potassium hydroxide was added. The mixture was evaporated under reduced pressure, and the product was washed with ethanol (2 × 20 ml.) and crystallised from 90% aqueous ethanol.

(*a*) *o*-Toluidine gave *potassium 2-amino*-m-*tolyl sulphate* (1·9 g.) as flat needles (Found: C, 35·4; H, 3·7; N, 5·6; S, 13·0; K, 15·9. $C_7H_8O_4NSK$ requires C, 34·9; H, 3·3; N, 5·8; S, 13·3; K, 16·2%).

This salt (500 mg.), in water (2 ml.) and concentrated hydrochloric acid (1 ml.), was heated to 100° for 30 min., and the solution was neutralised with 2N-sodium hydroxide. Extraction with ether and evaporation of the solvent yielded 2-amino-*m*-cresol (210 mg.); from light petroleum (b. p. 80—100°) it formed plates, m. p. 149—150° (Found: N, 11·1. Calc. for C_7H_9ON: N, 11·4%). Hodgson and Beard (*J.*, 1925, 498) report m. p. 150°. The *dibenzoate* crystallised from aqueous methanol in needles, m. p. 155—156° (Found: C, 75·6; H, 5·15; N, 4·1. $C_{21}H_{11}O_3N$ requires C, 76·1; H, 5·2; N, 4·2%).

When the dibenzoate (50 mg.) was heated to 210—220° for 3 hr., benzoic acid (10 mg.; m. p. and mixed m. p. 121°) sublimed. The residue was extracted with light petroleum (b. p. 60—80°) (2 ml.), the extract was washed with aqueous sodium hydrogen carbonate, and the solvent was evaporated. The product crystallised from aqueous ethanol to yield *4-methyl-2-phenylbenzoxazole* (25 mg.) as needles, m. p. 92—93° (Found: C, 80·7; H, 5·45; N, 7·15. $C_{14}H_{11}ON$ requires C, 80·4; H, 5·3; N, 6·7%).

(*b*) *m*-Toluidine gave *potassium 2-amino*-p-*tolyl sulphate* (Me = 4) (2·55 g.), as light brown elongated plates (Found: N, 5·6; S, 13·1. $C_7H_8O_4NSK$ requires N, 5·8; S, 13·3%).

When a solution of the salt (500 mg.), in water (2 ml.) and ethanol (1 ml.), stood with concentrated hydrochloric acid (0·5 ml.) for some hours, *2-amino*-p-*tolyl hydrogen sulphate* (260 mg.) separated. The acid was purified by dissolving it in N-sodium hydroxide and acidifying the solution; it formed needles, m. p. 286—288° (decomp.) (Found: C, 41·3; H, 4·5; N, 6·8; S, 16·3%; equiv., 198. $C_7H_9O_4NS$ requires C, 41·4; H, 4·5; N, 6·9; S, 15·8%; equiv., 203).

The ester (500 mg.) was hydrolysed as before, to yield 2-amino-*p*-cresol (226 mg.), separating

from light petroleum (b. p. 80—100°) in needles, m. p. 134—135° (Found: N, 11·5. Calc. for C_7H_9ON: N, 11·4%). Nölting and Kohn (*Ber.*, 1884, **17**, 351) report m. p. 135°. The dibenzoate formed needles (from aqueous ethanol), m. p. and mixed m. p. 191—192° (Found: C, 75·7; H, 5·4; N, 4·5. Calc. for $C_{21}H_{11}O_3N$: C, 76·1; H, 5·2; N, 4·2%), and the diacetate crystallised from light petroleum (b. p. 80—100°) in plates, m. p. and mixed m. p. 143—144° (Found: N, 6·7. Calc. for $C_{11}H_{13}O_3N$: N, 6·8%). Auwers and Czerny (*ibid.*, 1898, **31**, 2692) and Auwers and Eisenlohr (*Annalen*, 1909, **369**, 223) give m. p. 190—191° and 145° respectively for these derivatives.

(*c*) *p*-Toluidine gave *potassium* 6-*amino*-m-*tolyl sulphate* (3·2 g.) as light brown elongated plates (Found: N, 5·8%).

6-*Amino*-m-*tolyl hydrogen sulphate* (210 mg.) separated when the above salt (500 mg.), in water (2 ml.), was acidified with concentrated hydrochloric acid (0·5 ml.). The ester was purified by precipitation with acid from a solution in warm N-sodium hydroxide; it formed plates, m. p. 258—260° (decomp.) (Found: C, 41·2; H, 4·5; N, 6·8; S, 15·75%; equiv., 210).

The *sodium* salt (prepared from the acid) separated from water in light brown irregular plates (Found: N, 5·9; S, 14·7. $C_7H_8O_4NSNa$ requires N, 6·2; S, 14·2%).

The acid (500 mg.) was hydrolysed as before, to yield 6-amino-*m*-cresol (210 mg.), crystallising from light petroleum (b. p. 80—100°) in needles, m. p. 159—160° (decomp.) (Found: C, 68·5; H, 7·3; N, 11·0. Calc. for C_7H_9ON: C, 68·3; H, 7·4; N, 11·4%). Auwers, Borsche, and Weller (*Ber.*, 1921, **54**, 1291) give m. p. 157—159°, and Proskouriakoff and Titherington (*J. Amer. Chem. Soc.*, 1930, **52**, 3978), m. p. 162° (decomp.). The dibenzoate formed needles, m. p. 145—146°: after four recrystallisations from methanol it had m. p. 150° (Found: N, 4·3. Calc. for $C_{21}H_{17}O_3N$: N, 4·2%). Auwers, Borsche, and Weller (*loc. cit.*) report m. p. 152° after four, and m. p. 162—163° after six recrystallisations of this derivative from methanol. The *diacetate* crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 153—154° (Found: N, 6·5. $C_{11}H_{13}O_3N$ requires N, 6·8%).

When the dibenzoyl derivative (600 mg.) was heated to 220—230° for 4 hr., benzoic acid (130 mg.; m. p. and mixed m. p. 121°) sublimed. The residue was extracted with light petroleum (b. p. 60—80°), and evaporation of the solvent yielded 6-*methyl*-2-*phenylbenzoxazole* (302 mg.) as needles (from aqueous ethanol), m. p. 98—99° (Found: C, 80·5; H, 5·6; N, 6·5. $C_{14}H_{11}ON$ requires C, 80·4; H, 5·3; N, 6·7%). An ethanolic solution had a violet fluorescence in ultra-violet light.

Oxidation of the Aminobenzoic Acids.—The solution obtained as described above was acidified to pH 2 with 2N-sulphuric acid, and, after filtration, extracted with ether for 24 hr. The pH of the aqueous solution was adjusted to 6 with 2N-potassium hydroxide, and the solution was evaporated under reduced pressure. The residue was extracted with boiling methanol (4 × 50 ml.), and the combined extracts were evaporated to 50 ml. and treated with ether (150 ml.). After a few minutes the coloured precipitate was removed, ether (1 l.) was added to the filtrate during 2 hr., and the product was collected.

(*a*) Anthranilic acid gave a *monopotassium* salt (1·9 g.) of the sulphuric ester, slowly separating from aqueous ethanol in needles, m. p. 210—211° (decomp.) (Found: N, 5·3; S, 12·3; K, 14·8%; equiv., 275. $C_7H_6O_6NSK$ requires N, 5·2; S, 11·8; K, 14·4%; equiv., 271). When sodium persulphate (8·7 g.) was used in the oxidation, a *monosodium* salt was obtained as needles (from methanol–ether) (Found: N, 5·7. $C_7H_6O_6NSNa$ require N, 5·5%).

When the above solution was evaporated at pH > 7, the disalts of the sulphuric ester were obtained. The dipotassium salt formed a gum, but the *disodium* salt was obtained as needles (from methanol–ether) (Found: N, 5·0; S, 11·8. $C_7H_5O_6NSNa_2$ requires N, 5·05; S, 11·6%).

The above monopotassium salt (1 g.), in water (2 ml.) and concentrated hydrochloric acid (0·5 ml.), was kept overnight at 0°; 2-*amino*-3-*carboxyphenyl hydrogen sulphate* separated; from water it formed needles, m. p. 285—288° (decomp.) (Found: N, 6·0; S, 13·9%; equiv., 115. $C_7H_7O_6NS$ requires N, 6·0; S, 13·7%; equiv., 116). Solutions of the salts had a faint blue fluorescence in daylight, and a bright blue fluorescence in ultra-violet light.

The ester (1 g.) was hydrolysed with hydrochloric acid, and 2N-sodium hydroxide was added dropwise to the solution until crystals separated. 3-Hydroxyanthranilic acid (620 mg.), purified by precipitation with acid from a solution in aqueous sodium hydroxide containing a trace of sodium hydrogen sulphite, was obtained in needles, decomp. 230—250° (Found: C, 54·5; H, 4·9; N, 9·0. Calc. for $C_7H_7O_3N$: C, 54·9; H, 4·6; N, 9·15%). Methyl 3-hydroxyanthranilate, prepared from the acid with hydrogen chloride in methanol (Musajo, Spada, and Coppini, *J. Biol. Chem.*, 1952, **196**, 185), crystallised from light petroleum (b. p. 60—80°) in plates, m. p. and mixed m. p. 94° (Found: N, 8·2. Calc. for $C_8H_9O_3N$: N, 8·4%).

(*b*) *p*-Aminobenzoic acid gave a *monopotassium* salt (2·1 g.) of the sulphuric ester, separating from ether–methanol in needles (Found: N, 5·0; S, 11·8; K, 14·0%; equiv., 273). The salt (1 g.), in water (2 ml.), was kept overnight at 0° with concentrated hydrochloric acid (0·5 ml.). *2-Amino-5-carboxyphenyl hydrogen sulphate* (310 mg.) separated; from ether–ethanol it formed pale pink prismatic needles, m. p. 208—210° (decomp.) (Found: N, 6·3; S, 13·4%; equiv., 119).

The ester (500 mg.) was hydrolysed with hydrochloric acid, the pH of the solution was adjusted to 5 with 2N-sodium hydroxide, and the solution was extracted with ether. Evaporation of the ether afforded 4-amino-3-hydroxybenzoic acid (210 mg.), separating from aqueous ethanol or from ethanol–benzene in light brown needles, m. p. 210—211°, raised to 216—217° by three recrystallisations from aqueous ethanol (Found: N, 8·8%; equiv. 156. Calc. for $C_7H_7O_3N$: N, 9·15%; equiv., 153). Bray, Lake, Neale, Thorpe, and Wood (*Biochem. J.*, 1948, **42**, 434) give m. p. 226°, and Einhorn and Pfyl (*Annalen*, 1900, **311**, 43) m. p. 216°. The methyl ester, prepared from the acid with hydrogen chloride in methanol (cf. Musajo *et al.*, *loc. cit.*), crystallised from light petroleum (b. p. 60—80°) in plates, m. p. 119—120° (Found: N, 8·25. Calc. for $C_8H_9O_3N$: N, 8·4%). Einhorn *et al.* (*loc. cit.*) report m. p. 121° for methyl 4-amino-3-hydroxybenzoate.

Oxidation of Sulphanilic Acid.—The aqueous solution was acidified to pH 4 with 2N-sulphuric acid, and filtered, and the filtrate was washed with butanol (10 × 200 ml.). The pH of the solution was adjusted to 7 with 2N-potassium hydroxide, and the solution was evaporated under reduced pressure. The residue was extracted with boiling methanol (4 × 100 ml.), and the extracts were evaporated to 50 ml. and allowed to crystallise; a reddish-brown solid and a brown gum separated. Two crystallisations of the solid from 90% ethanol afforded the *dipotassium* salt of *2-amino-5-sulphophenyl hydrogen sulphate* (2·8 g.) as colourless elongated plates (Found: N, 3·8; K, 22·3. $C_6H_5O_7NS_2K_2$ requires N, 4·1; K, 22·6%).

When the above salt (750 mg.), in water (2 ml.) and concentrated hydrochloric acid (0·5 ml.), was kept for some hours, the *monopotassium* salt (480 mg.) separated; from water it formed needles, m. p. 293—294° (decomp.) (Found: N, 4·7; S, 21·0; K, 13·0%; equiv., 303. $C_6H_6O_7NSK$ requires N, 4·6; S, 20·9; K, 12·7%; equiv., 307).

When this salt (200 mg.) was heated to 100° for 30 min. with concentrated hydrochloric acid (1 ml.), 4-amino-3-hydroxybenzenesulphonic acid (92 mg.) separated; it crystallised from water in needles, m. p. >300° (Found: C, 38·0; H, 4·0; N, 7·2. Calc. for $C_6H_7O_4NS$: C, 38·1; H, 3·7; N, 7·4%).

The acid (500 mg.) slowly dissolved in a mixture of pyridine (2 ml.) and acetic anhydride (1 ml.). After 24 hr., the excess of the reagents was evaporated and the oil, in ethanol (2 ml.), was treated with dry ether at 0°. The solid was recrystallised four times from ether–ethanol, to yield *pyridinium 4-acetamido-3-acetoxybenzenesulphonate* (400 mg.) as prismatic needles, m. p. 156—158° (Found: N, 8·0, 7·9. $C_{15}H_{16}O_6N_2S$ requires N, 7·95%). A mixture with pyridinium 4-acetamido-2-acetoxybenzenesulphonate (m. p. 167—170°) had m. p. 138—143°.

4-Amino-2-hydroxybenzenesulphonic acid, prepared from *m*-aminophenol by the method of Thorpe and Williams (*loc. cit.*), crystallised from water in needles, m. p. >300° (Found: N, 7·55%). Doub *et al.* (*loc. cit.*) report m. p. 275°.

Oxidation of p-*Diphenylylamine.*—The aqueous solution obtained as described above was evaporated to 100 ml. under reduced pressure and filtered, and the filtrate was kept overnight at 0°. *Potassium 4-amino-3-diphenylyl sulphate* (225 mg.) separated; from aqueous ethanol it formed light brown plates (Found: N, 4·7; S, 10·9. $C_{12}H_{10}O_4NSK$ requires N, 4·6; S, 10·6%). With sodium persulphate the *sodium* salt was obtained, separating from aqueous ethanol in plates (Found: N, 4·9. $C_{12}H_{10}O_4NSNa$ requires N, 4·9%).

The filtrate was acidified with 2N-sulphuric acid and kept at 0° overnight, *4-amino-3-diphenylyl hydrogen sulphate* (610 mg.) separating; on repeated recrystallisation from aqueous ethanol it formed elongated plates, m. p. 292—293° (decomp.) (Found: C, 54·6; H, 4·4; N, 5·4; S, 11·8%; equiv., 259. $C_{12}H_{11}O_4NS$ requires C, 54·3; H, 4·2; N, 5·3; S, 12·1%; equiv., 265). The above acid (mixed m. p.) was also obtained when a suspension of the potassium salt in water was acidified. Solutions of the ester had a blue fluorescence in ultra-violet light.

The ester (500 mg.), in water (10 ml.), was heated to 100° with concentrated hydrochloric acid (3 ml.) for 30 min. Water (250 ml.) was added and the mixture was heated under reflux for 15 min. and filtered. 4-Amino-3-hydroxydiphenyl sulphate (280 mg.) separated from the filtrate in plates. The filtrate was neutralised with 2N-sodium hydroxide, when *4-amino-3-hydroxydiphenyl* (120 mg.) separated; from aqueous ethanol it formed plates, m. p. 182—184°

(Found : C, 77·6; H, 6·2; N, 7·5. $C_{12}H_{11}ON$ requires C, 77·8; H, 6·0; N, 7·6%). Ethanolic solutions had a light blue fluorescence in ultra-violet light.

The *dibenzoate* separated from aqueous ethanol or from light petroleum (b. p. 80—100°) in needles, m. p. 148—149° (Found : C, 79·2; H, 5·1; N, 3·4. $C_{26}H_{19}O_3N$ requires C, 79·4; H, 4·9; N, 3·6%). The *diacetate* crystallised from aqueous ethanol as needles, m. p. 123—124° (Found : N, 4·9. $C_{16}H_{15}O_3N$ requires N, 5·2%).

The dibenzoate (100 ml.) was heated to 200—210° for 6 hr.; benzoic acid (20 mg.; m. p. and mixed m. p. 121°) sublimed. The residual gum was extracted with light petroleum (b. p. 60—80°) (5 ml.), the solvent was evaporated, and the residue crystallised from aqueous ethanol, to give 2 : 6-*diphenylbenzoxazole* (55 mg.) as needles, m. p. 107° (Found : N, 5·0. $C_{19}H_{13}ON$ requires N, 5·2%), An ethanolic solution of the benzoxazole had a violet fluorescence in ultra-violet light.

Oxidation of p-*Bromoaniline*.—The aqueous solution was acidified with 2N-sulphuric acid, the precipitate was separated, the pH of the filtrate was adjusted to 7 with 2N-potassium hydroxide, and the solution was evaporated to dryness under reduced pressure. The residue was extracted with methanol (3 × 100 ml.), and the extract was evaporated to small bulk and allowed to crystallise. *Potassium* 2-*amino*-5-*bromophenyl sulphate* (1·9 g.) separated from 90% ethanol in flat needles (Found : N, 4·6; S, 10·5. $C_6H_5O_4NBrSK$ requires N, 4·6; S, 10·5%).

When the above salt (1 g.), in water (5 ml.), was kept overnight with concentrated hydrochloric acid (0·5 ml.), 2-*amino*-5-*bromophenyl hydrogen sulphate* was obtained; from water it formed greyish plates, m. p. 239—240° (decomp.) (Found : N, 5·3; S, 12·0%; equiv., 270. C_6H_6ONBrS requires N, 5·2; S, 12·0%; equiv., 268).

The *sodium* salt (prepared from the acid) crystallised from water in brownish irregular plates (Found : N, 4·55. $C_6H_5O_4NBrSNa$ requires N, 4·8%).

The ester (500 mg.) in water (2 ml.) was hydrolysed with hydrochloric acid (2 ml.) as before, and 2N-sodium hydroxide was added to the cooled solution until the product separated. 5-Bromo-*o*-aminophenol (190 mg.) crystallised from water in plates, m. p. 149·5—150·5° (Found : N, 7·5. Calc. for C_6H_6ONBr : N, 7·45%). Hodgson and Kershaw (*J.*, 1928, 2703) report m. p. 150°. The *dibenzoyl* derivative separated from aqueous methanol in needles, m. p. 133—134° (Found : C, 60·5; H, 3·7; N, 3·5. $C_{20}H_{14}O_3NBr$ requires C, 60·6; H, 3·6; N, 3·5%).

When the dibenzoyl derivative was heated to 220—225° for 3 hr., benzoic acid (m. p. and mixed m. p. 121°) sublimed, and the product was isolated with light petroleum (b. p. 60—80°). Evaporation of the solvent afforded 6-*bromo*-2-*phenylbenzoxazole*; from aqueous ethanol it formed pale pink plates, m. p. 104—105° (Found : N, 5·2; Br, 29·15. $C_{13}H_8ONBr$ requires N, 5·1; Br, 29·1%).

Oxidation of m-*Chloroaniline*.—The aqueous solution was treated as in the last experiment, and the product was isolated as before. *Potassium* 2-*amino*-4-*chlorophenyl sulphate* separated from aqueous ethanol in brownish plates (Found : N, 5·2; S, 12·2. $C_6H_5O_4NClSK$ requires N, 5·35; S, 12·25%).

Acidification of an aqueous solution of the potassium salt with hydrochloric acid yielded 2-*amino*-4-*chlorophenyl hydrogen sulphate*, slowly separating from water in prismatic needles, m. p. 268—271° (decomp.) (Found : N, 6·1; S, 14·1. $C_6H_6O_4NClS$ requires N, 6·3; S, 14·3%)

The acid ester was hydrolysed in the usual manner with hydrochloric acid, and the product was isolated with ether, to yield 4-chloro-*o*-aminophenol in plates (from water), m. p. 137° (Found : N, 9·7. Calc. for C_6H_6ONCl: N, 9·8%). Upson (*J. Amer. Chem. Soc.*, 1904, **32**, 40) reports m. p. 138°, and Mottier (*Arch. Sci. phys. nat.*, 1934, **16**, 301) m. p. 137·5—138·5°. The *dibenzoate* crystallised from aqueous ethanol in needles, m. p. 157—158° (Found : C, 68·25; H, 4·3; N, 3·9. $C_{20}H_{14}O_3NCl$ requires C, 68·3; H, 4·1; N, 4·0%).

Oxidation of o-*Nitroaniline*.—The aqueous solution was acidified with 10N-sulphuric acid, washed with ether (2 × 250 ml.), and extracted with butanol (8 × 150 ml.). The extract was dried (Na_2SO_4) and a slight excess of 2N-potassium hydroxide was added. The mixture was evaporated under reduced pressure and the dark residue was extracted with methanol (3 × 50 ml.). The methanolic extract was evaporated to small bulk and allowed to crystallise. The solid, in a minimum of methanol, was treated with an equal volume of ether. The coloured precipitate was filtered off and the residue was treated with excess of ether to yield *potassium* 2-*amino*-3-*nitrophenyl sulphate* (1·2 g.) as a yellow powder. After three recrystallisations from ether–methanol it formed yellow needles (Found : C, 26·4; H, 2·2; N, 10·0; S, 11·3. $C_6H_5O_6N_2SK$ requires C, 26·5; H, 1·85; N, 10·3; S, 11·3%).

The potassium salt was hydrolysed with hot hydrochloric acid, and the product was isolated with ether. 3-Nitro-*o*-aminophenol was obtained; from water it formed red needles, m. p.

210—212° (decomp.) (Found: N, 18·0. Calc. for $C_6H_6O_3N_2$: N, 18·2%). King (*J.*, 1927, 1058) gives m. p. 216—217° and Fourneau, Tréfouël, and Tréfouël (*Bull. Soc. chim.*, 1927, **41**, 448) give m. p. 212°.

We thank Mr. R. White for assistance with the anthranilic acid oxidations. Some analyses are by Mr. Oliver of the Microanalytical Laboratory, Imperial College of Science and Technology. This investigation has been supported by grants to the Royal Cancer Hospital and Chester Beatty Research Institute from the British Empire Cancer Campaign, the Jane Coffin Childs Memorial Fund for Medical Research, the Ann Fuller Fund, and the National Cancer Institute of the National Institutes of Health, U.S. Public Health Services.

THE CHESTER BEATTY RESEARCH INSTITUTE,
THE INSTITUTE OF CANCER RESEARCH, ROYAL CANCER HOSPITAL,
FULHAM ROAD, LONDON, S.W.3. [*Received, November 17th*, 1953.]

Triphenylmethane Derivatives from Condensations of Phenols with Hydroxybenzaldehydes.

By J. E. DRIVER and J. B. SOUSA.

[Reprint Order No. 4808.]

The preparation of various trihydroxytriphenylmethanes by the acid-catalysed condensation of phenols with aromatic hydroxy-aldehydes is described. The mechanism of reactions of this type is considered, and evidence is given of the intermediate formation of a dihydroxydiarylmethanol in two condensations, and the reversibility of some of the changes involved.

RUSSANOW (*Ber.*, 1889, **22**, 1943) obtained 4 : 4′-dihydroxytriphenylmethane by the acid-catalysed condensation of phenol with benzaldehyde and thus showed that aromatic aldehydes could behave in these condensations in a similar way to those aliphatic aldehydes which yield the corresponding dihydroxydiphenylmethanes.

The resins formed by condensation of phenols with aldehydes are in general regarded as resulting from repeated reactions of types (1) and (2) on the initial products from (1) and (2). In phenol–formaldehyde condensations the diphenylmethane derivatives formed are regarded as true intermediates for resin formation (Megson, *J. Soc. Chem. Ind.*, 1939, 131); T. T. Jones (*ibid.*, 1946, 264) claims, however, that at lower temperatures and with equimolecular proportions of phenol and formaldehyde the resinification may also proceed through formation of dialcohols by the further addition of a molecule of formaldehyde to the phenolic alcohol formed by (1).

$$R{\cdot}CHO + C_6H_5{\cdot}OH = R{\cdot}CH(OH){\cdot}C_6H_4{\cdot}OH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$HO{\cdot}C_6H_5 + R{\cdot}CH(OH){\cdot}C_6H_4{\cdot}OH = HO{\cdot}C_6H_4{\cdot}CHR{\cdot}C_6H_4{\cdot}OH + H_2O \quad . \quad . \quad . \quad (2)$$

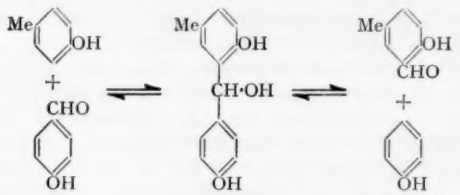
Isolation of the intermediate alcohol [as in (1)] is usually achieved only when the phenol is of lowered reactivity (Fishman, *J. Amer. Chem. Soc.*, 1920, **42**, 2288) or with special aldehydes (Balfe and Webber, *J.*, 1942, 718); various attempts have been made to prove the formation of the intermediate alcohol indirectly [Michael, *J. pr. Chem.*, 1898, (ii), **334**; von Euler and Kispeczy, *Z. physikal. Chem.*, 1941, *A*, **189**, 109].

Previously, only resinous products have been obtained by the condensation of phenol with *o*- or *p*-hydroxybenzaldehyde (Liebermann and Schwarzer, *Ber.*, 1876, **9**, 800; Trzcinski, *Ber.*, 1883, **16**, 2835; Zulkowski, *Monatsh.*, 1884, **5**, 108; Driver, *J. Soc. Chem. Ind.*, 1927, 197T). It is now shown that, at relatively low temperatures and in a suitable medium, triphenylmethane derivatives can be readily prepared by the acid-catalysed condensation of phenol and the cresols with various aromatic hydroxy-aldehydes, although in most of the reactions amorphous resins remain the chief product. The reactions at comparable stages are more complex than those with aliphatic or simple aromatic aldehydes, since the intermediate alcohol (1) (for example) contains two phenolic hydroxyl groups so providing additional activated positions for further condensation.

A 12% yield of 4 : 4′ : 4″-trihydroxytriphenylmethane (leucaurin) was isolated from the resin resulting from the condensation of phenol with *p*-hydroxybenzaldehyde, but no crystalline compound could be isolated from the products from phenol with *o*- or *m*-hydroxybenzaldehyde. All three hydroxybenzaldehydes condensed with *o*-cresol to give triphenylmethane derivatives: notably, *o*-cresol and *p*-hydroxybenzaldehyde gave an 80% yield of 4 : 4′ : 4″-trihydroxy-3 : 3′-dimethyltriphenylmethane. Triphenylmethane derivatives were also obtained from the condensations of phenol and *o*-methoxybenzaldehyde, phenol and 2-hydroxy-5-methylbenzaldehyde, and *m*-cresol and *p*-hydroxybenzaldehyde.

The yields give some indication of the effect of orientation of phenolic hydroxyl groups on the course of the reaction. In no reaction in which the hypothetical intermediate alcohol or the triphenylmethane product has a free position *para* to a hydroxyl group was any other than a small yield of crystalline compound obtained. Diminution of yield as a result of resin formation is much less apparent where methoxyl groups are concerned: *o*-methoxybenzaldehyde and phenol gave a 21% yield of the expected triphenylmethane compound, and with *p*-methoxybenzaldehyde and anisole (no free positions *para* to methoxyl) a 95% yield of 4 : 4′ : 4″-trimethoxytriphenylmethane is readily obtained. That neither chelation nor steric hindrance can account for the apparent non-formation of triphenylmethane derivatives from, for example, phenol and salicylaldehyde is shown by the reaction between phenol and 2-hydroxy-5-methylbenzaldehyde, which is also chelated but has no free position *para* to the hydroxyl group.

In the condensations of phenol with 2-hydroxy-5-methylbenzaldehyde and of *p*-cresol with *p*-hydroxybenzaldehyde, where a common intermediate alcohol is postulated (only *ortho* condensation being possible in the second reaction), it was found possible to isolate in the early stages a compound, common to both reactions, which had the expected elementary composition and molecular weight. This provides the first clear indication that the formation of triphenylmethane derivatives in these reactions follows courses (1) and (2). In each condensation the aldehyde from the other reaction was also formed:



There is earlier evidence that reactions of this kind may be reversible, since Ziegler, Meralla, and Simmler (*Ber.*, **1943**, **76**, *B*, 664) found that pure 2-hydroxymethyl-4 : 6-dimethylphenol in acid media gave some di-(2-hydroxy-3 : 5-dimethylphenyl)methane, a process which they accounted for by the supposed reversible fission of the first compound into 2 : 4-dimethylphenol and formaldehyde.

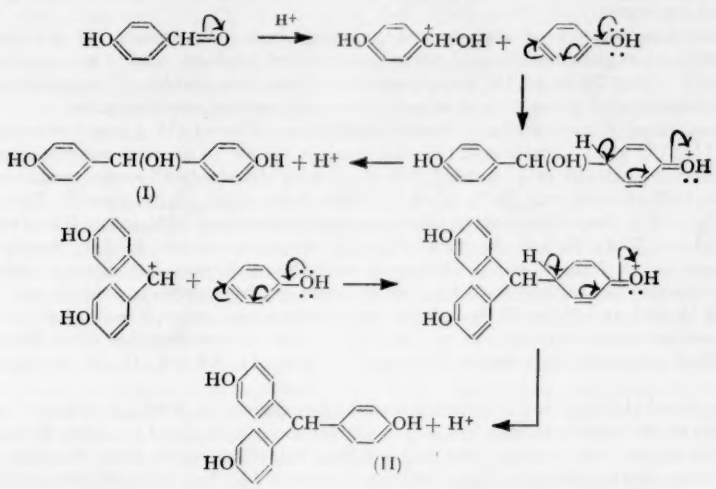
The behaviour in acid media of the intermediate alcohols is of considerable interest. A parallel series of alcohols (the methoxydiphenylmethanols) has been studied by Kenyon and his collaborators (*J.*, **1942**, 605; **1951**, 386; **1952**, 790, 4964). These compounds tend to yield carbonium ions by alkyl–oxygen fission in acid media, a tendency enhanced by the mesomeric effects of *o*- and *p*-methoxyl substituents convergent on the carbinol carbon atom. In comparable dihydroxydiphenylmethanols the change would be:

$$(HO{\cdot}C_6H_4)_2CH{\cdot}OH + H_2SO_4 = (HO{\cdot}C_6H_4)_2\overset{+}{C}H + H_2O + HSO_4^-$$

In phenol–hydroxybenzaldehyde condensations the formation of deep colours on the addition of a few drops of sulphuric acid to glacial acetic acid solutions of the reactants may indicate the presence of carbonium ions.

The formation of triphenylmethane derivatives from phenols and hydroxybenzaldehydes *via* the intermediate alcohols may be represented as in the following example; the mechanism in the second stage [formation of (II) from (I)] is analogous to that suggested for the

formation of 2 : 4 : 6 : 2′ : 4′ : 6′-hexamethoxytriphenylmethane from 1 : 3 : 5-trimethoxybenzene and 2 : 4 : 6-trimethoxydiphenylmethanol (Kenyon and Mason, *J.*, 1952, 4964) :



Experimental

The sulphuric acid used was 36N.

Condensation of Phenol and p-*Hydroxybenzaldehyde.*—Sulphuric acid (30 ml.) in glacial acetic acid (50 ml.) was added to phenol (96·3 g.) and *p*-hydroxybenzaldehyde (50 g.) in glacial acetic acid (300 ml.) at 0° with constant stirring. A red colour developed (this was observed also in other condensations). The solution was kept at 10° for 70 hr. and then poured on a mixture of crushed ice and water. The red resin, after having been washed free from phenol and acid, formed a hard mass. Isolation of crystalline material was achieved by extraction with dilute ethanol. The extracts were cooled slowly, whereupon droplets of resin separated; rapid filtration and further cooling caused the deposition of feathery crystals of 4 : 4′ : 4″-trihydroxytriphenylmethane (leucaurin) (10·4 g.), m. p. 239—240°, which separated in large crystals from mixed solvents but persistently retained an orange tint (Found: C, 77·5; H, 5·3. Calc. for $C_{19}H_{16}O_3$: C, 78·0; H, 5·4%). The triacetyl derivative had m. p. 128° (Found: C, 71·7; H, 5·5; Ac, 31·3%; *M* in benzene, 394. Calc. for $C_{25}H_{22}O_6$: C, 71·7; H, 5·3; Ac, 30·9%; *M*, 418). The trimethyl ether, prepared by methylation with methyl sulphate and sodium hydroxide, had m. p. and mixed m. p. with an authentic sample 48—49° (Found: C, 78·2; H, 6·9; OMe, 25·2. Calc. for $C_{22}H_{22}O_3$: C, 79·0; H, 6·6; OMe, 27·7%). Oxidation of the leucaurin with alkaline permanganate yielded traces of brown needles, m. p. 230—232° (possibly aurin, though there is no record of this reaction in the literature).

The resins obtained in the following condensations were treated in a similar way unless otherwise stated.

Condensation of Phenol and m-*Hydroxybenzaldehyde.*—Phenol (21·8 g.) was condensed with *m*-hydroxybenzaldehyde (10·7 g.) in glacial acetic acid (50 ml.) by means of sulphuric acid (6 ml.) in glacial acetic acid (12 ml.). The brittle olive-black resin isolated after 36 hr. at 10° yielded no crystalline compound, and the acetylated product (*M*, 590. Calc.: 418) also could not be crystallized.

Condensation of Phenol and Salicylaldehyde.—Phenol (50 g.) and salicylaldehyde (26 g.) in glacial acetic acid (125 ml.) were treated with sulphuric acid (15 ml.) in glacial acetic acid (25 ml.), and the mixture kept at 15° for 72 hr. Uncrystallizable red resin only was obtained, and the product on methylation yielded an uncrystallizable substance (*M*, 735. Calc.: 334). Condensations with larger proportions of phenol at 10° for times varied from 6 to 75 hr. yielded no crystalline product.

That the apparent non-formation of 2 : 4′ : 4″-trihydroxytriphenylmethane was not due to self-condensation of salicylaldehyde was shown by the following experiment. Salicylaldehyde (5 g.) in glacial acetic acid (25 ml.) was treated with sulphuric acid (3 ml.) in glacial acetic acid

(5 ml.). After 48 hr. at 10° the mixture was shaken with water, and phenol and salicylaldehyde were removed from the non-aqueous layer by extraction with chloroform. A small quantity (*ca.* 0·08 g.) of uncrystallizable red resin was obtained, most of the phenol and salicylaldehyde having been recovered.

Attempted Condensation of Anisole and Salicylaldehyde.—To anisole (24 g.) and salicylaldehyde (12·2 g.) in glacial acetic acid (50 ml.) was added sulphuric acid (6 ml.) in glacial acetic acid (10 ml.). After 72 hr. at 10° no appreciable change was visible. This condensation was not further investigated as reaction at suitably low temperatures was very slow.

Condensation of Phenol and o-*Methoxybenzaldehyde.*—Phenol (19 g.) and *o*-methoxybenzaldehyde (11 g.) in glacial acetic acid (60 ml.), kept at 10° for 70 hr. with sulphuric acid (6 ml.) in glacial acetic acid (10 ml.), yielded 6·5 g. of 4 : 4′-*dihydroxy*-2″-*methoxytriphenylmethane*, m. p. 181—183° (Found : C, 78·7; H, 5·7; OMe, 9·0. $C_{20}H_{18}O_3$ requires C, 78·4; H, 5·9; OMe, 10·1%). The *diacetyl* derivative, after recrystallization from 95% ethanol, had m. p. 105—106° (Found : C, 73·4; H, 5·5; Ac, 22·4. $C_{24}H_{22}O_5$ requires C, 73·8; H, 5·6; Ac, 22·1%).

Condensation of Phenol and 2-*Hydroxy*-5-*methylbenzaldehyde.*—(*a*) Phenol (8·7 g.) and 2-hydroxy-5-methylbenzaldehyde (5·4 g.) were condensed by sulphuric acid (3 ml.) in glacial acetic acid (5 ml.) at 10° for 70 hr. From the product was isolated 0·51 g. of 2 : 4′ : 4″-*trihydroxy*-5-*methyltriphenylmethane*, m. p. 209—210° after recrystallization from dilute ethanol from which it separated in rosettes (Found : C, 78·0; H, 5·6. $C_{20}H_{18}O_3$ requires C, 78·4; H, 5·9%).

(*b*) To phenol (15·3 g.) and 2-hydroxy-5-methylbenzaldehyde (9·65 g.) in glacial acetic acid (50 ml.) was added sulphuric acid (4·8 ml.) in glacial acetic acid (5 ml.). After 20 hr. at 0° the solution was diluted with water. The resinous layer was dissolved in ether, the ether removed, and the residue steam-distilled. The distillate contained 2-hydroxy-5-methylbenzaldehyde and traces of anhydrobis-6-*m*-hydroxytolualdehyde, m. p. 141° (insoluble in alkali). The residual aqueous solution (with resin) was filtered rapidly; the filtrate when allowed to cool slowly deposited crystals (0·2 g.) of 2 : 4′-*dihydroxy*-5-*methyldiphenylmethanol*, m. p. 175—180° (decomp.) raised to 183—184° (decomp.) by three recrystallizations from dilute ethanol (Found : C, 73·4; H, 6·1%; *M* in benzene, 225. $C_{14}H_{14}O_3$ requires C, 73·0; H, 6·1%; *M*, 230).

(*c*) Phenol (6·9 g.) and 2-hydroxy-5-methylbenzaldehyde (4·9 g.) in glacial acetic acid (25 ml.) were kept with sulphuric acid (2·4 ml.) in glacial acetic acid (6·1 ml.) at 6° for 14 hr. After treatment similar to that in the previous experiment there was obtained a crystalline deposit which by fractional crystallization was separated into 2 : 4′ : 4″-trihydroxy-5-methyltriphenylmethane, m. p. 209—210°, and a small quantity of 2 : 4′-dihydroxy-5-methyldiphenylmethanol, m. p. 183—184° (decomp.). Concentration of the filtrate from the first recrystallization yielded prisms (0·093 g.) of *p*-hydroxybenzaldehyde, m. p. 114—115° undepressed in admixture with an authentic sample of m. p. 115—116°.

Condensation of o-*Cresol and* p-*Hydroxybenzaldehyde.*—To *o*-cresol (30 g.) and *p*-hydroxybenzaldehyde (15·5 g.) in glacial acetic acid (50 ml.) was added sulphuric acid (6 ml.) in glacial acetic acid (10 ml.). The mixture set to a sludgy mass within an hour. It was kept for a further 12 hr. at the same temperature (10°) and filtered. The residue was boiled thrice with water, and then yielded 4 : 4′ : 4″-*trihydroxy*-3 : 3′-*dimethyltriphenylmethane* (32·5 g.), m. p. 245—246° (Found : C, 78·7; H, 6·6. $C_{21}H_{20}O_3$ requires C, 78·7; H, 6·2%). The *triacetyl* derivative had m. p. 185° after recrystallization from 95% ethanol (Found : C, 72·9; H, 5·8; Ac, 28·9. $C_{27}H_{26}O_6$ requires C, 72·6; H, 5·8; Ac, 28·9%).

Condensation of o-*Cresol and* m-*Hydroxybenzaldehyde.*—To *o*-cresol (35 g.) and *m*-hydroxybenzaldehyde (17·6 g.) in glacial acetic acid (55 ml.) was added sulphuric acid (6 ml.) in glacial acetic acid (12 ml.), and the mixture was kept at 10° for 36 hr. The resin yielded prisms of 3 : 4′ : 4″-*trihydroxy*-3′ : 3″-*dimethyltriphenylmethane* (0·8 g.), m. p. 162° after recrystallization from dilute ethanol (Found : C, 78·8; H, 6·5%).

Condensation of o-*Cresol and Salicylaldehyde.*—*o*-Cresol (34·9 g.) and salicylaldehyde (19·5 g.) in glacial acetic acid (60 ml.) were kept with sulphuric acid (10 ml.) in glacial acetic acid (20 ml.) at 10° for 70 hr. The resin yielded yellowish crystals of 2 : 4′ : 4″-*trihydroxy*-3′ : 3″-*dimethyltriphenylmethane* (0·07 g.), m. p. 236° (Found : C, 77·7; H, 6·4%).

Condensation of m-*Cresol and* p-*Hydroxybenzaldehyde.*—*m*-Cresol (25·6 g.) and *p*-hydroxybenzaldehyde (12·75 g.) were kept with sulphuric acid (6 ml.) in glacial acetic acid (10 ml.) at 11° for 40 hr. Excess of *m*-cresol was removed by steam-distillation. From the residual resin was isolated 4 : 4′ : 4″-*trihydroxy*-2 : 2′-*dimethyltriphenylmethane* (0·69 g.) in crystals, m. p. 205°, which became red on exposure to air (Found : C, 78·0; H, 6·6%). The *triacetyl* derivative had m. p. 185° after recrystallization from 95% ethanol (Found : C, 72·5; H, 5·7%).

Condensation of p-*Cresol and* p-*Hydroxybenzaldehyde.*—(*a*) *p*-Cresol (10·5 g.) and *p*-hydroxybenzaldehyde (5 g.) in glacial acetic acid (30 ml.) were kept with sulphuric acid (3 ml.) in glacial acetic acid (5 ml.) at 10° for 70 hr. Traces of a substance, m. p. 173—175°, were isolated (Found: C, 74·1; H, 6·5. Calc. for $C_{21}H_{20}O_3$: C, 78·7; H, 6·2. Calc. for $C_{14}H_{14}O_3$: C, 73·0; H, 6·1%).

(*b*) A solution of *p*-cresol (45 g.) and *p*-hydroxybenzaldehyde (10·2 g.) in glacial acetic acid (50 ml.) was kept with sulphuric acid (5·5 ml.) in glacial acetic acid (4·5 ml.) at 4·5° for 70 hr. It was then diluted with ice-water, and the resinous layer was steam-distilled. The distillate contained 2-hydroxy-5-methylbenzaldehyde, which was isolated (0·331 g.), after extraction with ether, *via* the sodium bisulphite compound; it then had m. p. 55—56°, unchanged in admixture with an authentic sample.

The aqueous liquid remaining from the steam distillation was separated from most of the resin and extracted with ether. After removal of the ether, slow cooling of a hot solution of the residue in 10% ethanol yielded first a little resin, and then faintly pink crystals (0·18 g.) of 2 : 4′-dihydroxy-5-methyldiphenylmethanol, m. p. 179—181° (decomp.) raised by recrystallization to 181—183° (decomp.) undepressed in admixture with the compound obtained in the condensation of phenol with 2-hydroxy-5-methylbenzaldehyde. A further small quantity of the same compound was obtained by extracting with dilute ethanol the residual resin from the steam-distillation.

Condensation of Anisole and Anisaldehyde.—Anisole (18 g.) and anisaldehyde (9·5 g.) in glacial acetic acid (40 ml.) were kept with sulphuric acid (18 ml.) and glacial acetic acid (15 ml.) at 11° for 2 weeks: by this time the whole mass had become semi-solid. Vacuum-distillation of the product made in this way is unnecessary (cf. Baeyer and Villiger, *Ber.*, 1902, **35**, 1197). After having been shaken successively with water, sodium hydroxide solution, and water, the product was recrystallized from 95% ethanol, yielding 4 : 4′ : 4″-trimethoxytriphenylmethane (20 g.), m. p. 48—49° after two recrystallizations.

UNIVERSITY OF HONG KONG, HONG KONG. [*Received, November 17th*, 1953.]

The Complex-forming Behaviour of Tin, Germanium, and Titanium with Some Dibasic Carboxylic Acids.

By G. MATTOCK.

[Reprint Order No. 4703.]

The conflicting reports of previous workers on complex formation between Sn(IV), Ge(IV), and Ti(IV) and tartaric acid have led to a re-examination of the problem, by electrometric, polarimetric, and polarographic methods.

Metal : tartrate combining ratios of 1 : 1 and 1 : 2, and possibly 1 : 4, are demonstrated for tin; 1 : 1, 1 : 2, and possibly 2 : 1 for germanium; and evidence is obtained of 2 : 1, 1 : 1, and 1 : 2 for titanium, although here many species (*e.g.*, polynuclear) may co-exist. The predominance of any complex depends on the conditions; the solutions are often colloidal. In this connection, the ageing properties of the complex solutions are described and discussed.

The complicating effects of hydrolysis restrict quantitative interpretation, particularly from electrometric measurements. These supply indications, however, that complex-forming characteristics of the three metals examined are the same in tartaric, malic, and succinic acid solutions.

A value for the concentration equilibrium constant between the chloro- and monotartrato-complexes of tin is calculated from polarographic data.

A SURVEY of the literature on the tartrate complexes of tin(IV) and titanium(IV), of importance in analytical chemistry, reveals several apparently conflicting results; and germanium(IV), which bridges the two metals in the sub-groups IVA and IVB of the Periodic Table, has only recently been studied in tartrate solutions (Vartapétian and Tchakirian, *Compt. rend.*, 1953, **236**, 81). These systems were therefore examined further to correlate existing data.

Earlier workers were chiefly concerned with attempts at isolation of complexes. Thus Henderson, Orr, and Whitehead (*J.*, 1899, **75**, 542) prepared substances of composition claimed to be $M^{IV}O(C_4H_4O_6M^I)_2,xH_2O$, where $M^{IV} = Sn^{IV}$ or Ti^{IV}, and M^I = Na, K, or NH_4.

Rosenheim and his co-workers (*Z. anorg. Chem.*, 1904, **39**, 170; 1901, **26**, 239) obtained products containing tin and tartrate combined in the ratio 1 : 1, and various gelatinous titanium compounds with titanium : tartrate ratios of 2:1, 2:3, and 1:2, the product obtained depending on the conditions. It is very doubtful whether these substances were homogeneous, however, in view of the preparative methods employed and the fact that extraction by alcohol frequently altered their composition. Other authors have expressed similar doubts in analogous circumstances (Dey, *J. Colloid. Sci.*, 1948, **3**, 472, and references therein); Dey has pointed out that these complex solutions are frequently colloidal, and so isolated products are liable to be indefinite. Dumanski and Kniga (*Kolloid-Z.*, 1928, **44**, 273) and Haïssinsky and Yang Jeng-Tsong (*Analyt. Chim. Acta*, 1949, **3**, 422) noted that solutions of high metal : tartrate ratio are colloidal, but ionic at higher tartrate concentrations (Dumanski and Kniga, *loc. cit.*).

In contrast to Rosenheim's conclusion of 1 : 1 combination (see above), Zolotukhin (*J. Gen. Chem., U.S.S.R.*, 1949, **19**, 983) has decided, from titration experiments, that 1 : 2 is the combining ratio between tin and tartrate. It may be noted that polarographic studies on the stannous–tartrate system (Lingane, *J. Amer. Chem. Soc.*, 1943, **65**, 866) were suggestive of the existence of two complexes in solution. The effects of dilution (Grossmann, *Ber.*, 1905, **38**, 711) and of hydrogen-ion concentration (Schenk, *Helv. Chim. Acta*, 1936, **19**, 639) on the titanium–tartrate system were examined polarimetrically, employing the 1 : 2 formulation, although Caglioti and Sartori (*Gazzetta*, 1936, **66**, 741) give the titanium : tartrate ratio as 2 : 3 in alkaline solution, and 1 : 1, shifting to 1 : 2 on dilution, in acid solution. Caglioti's work has been strongly criticised on theoretical grounds, however (Fouchay and Saucherre, *Bull. Soc. chim.*, 1947, 529).

The recent work of Vartapétian and Tchakirian (*loc. cit.*) on germanium(IV) oxide complexes with tartaric acid suggested 1 : 1 combination. Their investigations (published since completion of the present work) have been extended to a wider range of conditions, giving further information on the system (see below). This study used pH, polarimetric, and polarographic measurements.

Experimental

Much of the earlier work had apparently been vitiated by pre-reaction hydrolysis, so in order to enable the complex-forming ions to participate at least initially in competitive ionic equilibria, 4—5M-hydrochloric acid solutions were employed wherever practicable. Suitable adjustments to the acidity were made after the addition of complex-forming acid.

The tin used was in the form of ammonium hexachlorostannate, purified by double recrystallisation from a filtered solution in constant-boiling hydrochloric acid. It was used either as the solid (analysis for tin gave 99·88—100·0% of theoretical for various samples), or in 5N-"AnalaR" hydrochloric acid solution. A stock germanium solution was prepared by distilling germanium tetrachloride from spectrographically pure germanium dioxide in constant-boiling hydrochloric acid into similar acid, and standardised by the tannin method (Holness, *Analyt. Chim. Acta*, 1948, **2**, 254). Titanium was brought into solution by fusing the pure dioxide with potassium hydrogen sulphate and leaching the cooled melt with 3N-sulphuric acid. The titanium in the filtered solution was precipitated with ammonia, and the precipitate washed with 2% ammonium chloride solution and redissolved in 1 : 1 "AnalaR" hydrochloric acid, this procedure being repeated until the final solution was sulphate-free. Other materials used (tartaric and succinic acids, sodium hydroxide, and freshly-filtered ammonia) were all of "AnalaR" quality. The malic acid solutions were filtered before use to remove traces of insoluble matter.

The free acid content of titanium and germanium solutions could not be determined with any degree of accuracy, owing to hydrolysis and consequent liberation of acid brought about by addition of base in standardisation. An estimate was obtained by direct titration to the methyl-orange change with ammonia. This quantity, required in the polarimetric measurements, was adequately accurate, since in any given series the final acidity or alkalinity, calculated from the figure, was constant, so that the results in the series were comparable.

The commercial instruments used were a Cambridge Instrument Co. portable pH meter and glass electrode assembly (standardised by means of two buffer solutions of pH 4·00 and 9·20); a half-field polarimeter measuring to 0·01°, manufactured by Messrs. Bellingham and Stanley, Ltd. (the sodium-D lines were used as light source); and a Cambridge Instrument Co. pen-recording polarograph.

pH *Measurements.*—Titration experiments were carried out at a metal concentration of 10^{-3}M. Preliminary titrations with sodium hydroxide showed that the normal "additive" technique led to non-reproducibility, and consequently the "static" method was adopted, consisting in making up a series of solutions for a given titration curve, alkali content varying but the volume remaining constant. To the acid solution of the metal (suitably diluted immediately before use), the complexing acid was added, and diluted appropriately with water. After 2 min. from addition of acid, sodium hydroxide solution was added, to bring the total volume to 100 ml., and the glass electrode system inserted. The pH was measured after 4 min. from addition of acid; within 10 min. it was usually steady (see Results). Blank curves on the metal solution alone were obtained in a similar manner. All measurements were made at room temperature.

Polarimetric Measurements.—Job's method of continuous variations (*Ann. Chim.*, 1928, **9**, 113) was employed to determine the composition of the complexes formed, the enhanced optical rotatory power being used as a measure of complex formation. Behaviour at two total (metal + acid) concentration levels was investigated, $5{\cdot}0 \times 10^{-2}$M and 1·0M, except for germanium, where it was found not possible to prepare a stock chloride solution of sufficient concentration for a 1·0M-series. To the metal solution (or hexachlorostannate) varying quantities of freshly prepared (+)-tartaric acid solution were added, followed by water and ammonia solution to bring the final solution to a volume of 20 ml., and the desired acidity. All measurements were made at 20·0° ± 0·5°, this control being sufficient to prevent temperature variation errors. The tin and germanium solutions showed no variation in activity over a period of 30 min., during which time measurements could easily be effected. Titanium solutions required greater control, however (see Results).

Polarographic Measurements.—The cell used was a modification of the conventional low-resistance H-type, having a saturated calomel electrode as reference in one limb (Lingane and Laitinen, *Ind. Eng. Chem. Anal.*, 1939, **11**, 504). The cross-piece was set at an angle to the horizontal, to prevent streaming of the solutions in each limb owing to movement of the agar plug (Komyathy, Malloy, and Elving, *Analyt. Chem.*, 1952, **24**, 431); plug renewal was facilitated by incorporating a ground-glass joint. Electrical leakages into the earthed thermostat-bath water (all polarograms were recorded with the cell and contents at 25·00° ± 0·02°) were prevented by sealing the joint with vaseline.

Air was removed from the solutions investigated by passage for 20 min. of a stream of nitrogen, previously purified by bubbling through an alkaline solution of sodium dithionite (hydrosulphite) containing some sodium anthraquinone-β-sulphonate (Fieser's solution), and then through water.

Results

(I) *Tin.*—(a) pH *Measurements.* Despite close control, it was not possible to obtain a reproducible titration curve with a tin : tartrate ratio of 1 : 2, the complex solution being titrated against sodium hydroxide. Up to pH ~ 5·5, the curve was smooth, but in more alkaline conditions the pH varied erratically with time; *e.g.*, in 30 min. the pH of one solution rose from 8·15 to 8·46.

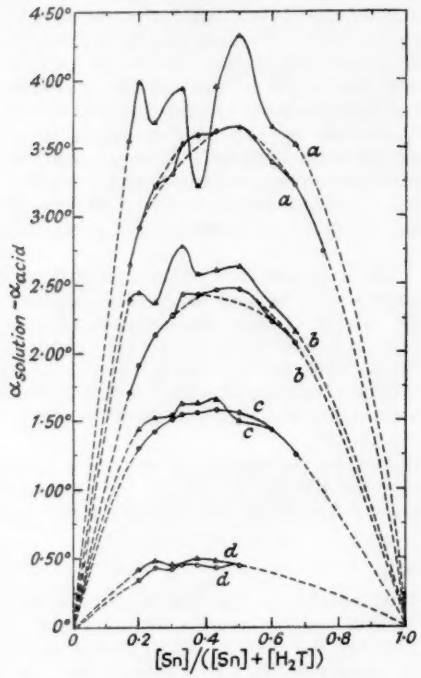
Absorption of carbon dioxide or attack on the vessel walls would have had the opposite effect; the phenomenon may have been due to slow desorption of hydroxyl ions during aggregation of micellar particles. Thus deposition of solid occurred above pH ~6, it being immediate above pH ~8.

(b) *Polarimetric measurements.* Measurements of ($\alpha_{\text{complex solution}} - \alpha_{\text{acid}}$) in the dilute series gave no definite maximum attributable to one complex when plotted against the solution composition, [Sn]/([Sn] + [tartaric acid]) (tartaric acid is henceforth referred to as H_2T). Such indefinite characteristics may be ascribed to the presence of more than one complex in solution. Vosburgh and Cooper (*J. Amer. Chem. Soc.*, 1941, **63**, 437) have shown, however, that when the property measured is sufficiently sensitive to change in complex concentration, then if the various species are easily interconvertible, identifiable maxima occur, displaced only slightly, if at all, from the true composition of the complexes to which they correspond. This was realised in more concentrated solutions, where separation is effected (Fig. 1). Two maxima are evident, at tin : tartrate ratios of 1 : 1 and 1 : 2, displaced and flattened somewhat from the effect of one maximum on the other. The broken lines represent extrapolations illustrating the situation where one species predominates. As the hydrochloric acid molarity increases, the extent of complex formation decreases (competitive action), and the 1 : 2 complex apparently becomes more predominant. These experimental results were fully reproducible.

In this series, solid hexachlorostannate was used (hydrochloric acid being added to reach the formal acidity), and considerable liberation of acid takes place on dissolution in the complexing acid. Since the optical rotatory power of free (+)-tartaric acid is affected by strong acids, the value of ($\alpha_{\text{complex solution}} - \alpha_{\text{acid}}$) is affected. By titration to the methyl-orange change with ammonia, this liberated acid was roughly estimated, and the corrections applied for in Fig. 1. It should be noted, however, that the positions of the maxima were the same on the " uncorrected " curve, where acid liberation was not allowed for.

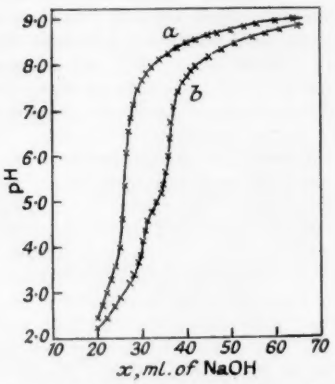
Effects of ageing. Ageing invariably caused an increase in the optical activity of the complex solutions (Fig. 1), it being most significant at the maxima. In the dilute ammoniacal

FIG. 1. *Optical activity variation curves for tin and tartaric acid.*



O = Fresh solutions. Δ = Aged solutions.
(*a*) Sn–H_2T. (*b*) Sn–H_2T, 0·5N in HCl.
(*c*) Sn–H_2T, 0·9N in HCl. (*d*) Sn–H_2T, 1·8N in HCl.

FIG. 2. pH *Titration curves of germanium.*



x Ml. of 0·082N-NaOH against 1 × 10^{-4} mole of Ge (in 10 ml.) +
(*a*) (90 − x) ml. of H_2O.
(*b*) 8·0 ml. of 0·05M-H_2T + (82 − x) ml. of H_2O.

series, many of the solutions became turbid quite rapidly after the first measurement, and after 1 day had deposited (presumably) basic tin tartrate. Solutions of higher tartrate content did not show such rapid changes, but deposition had occurred after 3 months. A new maximum is observable, corresponding to a 1[tin] : 4[tartrate] complex, presumably not present in sufficient amounts to affect the curve given by measurements on the fresh solutions.

(c) *Polarographic measurements.* No reduction wave is produced in alkaline, neutral, or acid stannic–tartrate solutions; apparently the rate of reduction of the complex ions is too slow for any appreciable reduction to occur during the short life of a mercury drop. Lingane (*J. Amer. Chem. Soc.*, 1945, **67**, 919) has shown that stannic tin produces a well-defined doublet wave in solutions approximately 4M with respect to chloride ions (M in hydrochloric acid), corresponding to $SnCl_6^{--} \longrightarrow SnCl_4^{--}$ (−0·25 v against S.C.E.), followed by $SnCl_4^{--} \longrightarrow$ metal (−0·52 v against S.C.E.). The combined diffusion currents are proportional to the tin concentration. Addition of tartaric acid reduces the tin concentration, and hence the total diffusion current, by complex formation. For the equilibrium $SnCl_6^{--} + m\text{HT}^- \rightleftharpoons SnCl_{6-m}(\text{HT})_m^{--} + m\text{Cl}^-$, HT^- being assumed to be the complex-forming species, the classical equilibrium constant is given by

$K = [SnCl_{6-m}(HT)_m^{--}][Cl^-]^m/[SnCl_6^{--}][HT^-]^m$. Experimentally, $[SnCl_{6-m}(HT)_m^{--}]/[SnCl_6^{--}]$ is determinable by measuring the diffusion current before and after addition of tartaric acid, while $[Cl^-]$ and $[HT^-]$ are known, and kept constant in a given run. By varying $[HT^-]$, two equations are obtained from which the two unknowns, K and m, may be evaluated, *on the assumption that* m (an average combining ratio) *does not vary on change of* $[HT^-]$.

The values of K and m, $1{\cdot}2 \times 10^3$ and 1·03 (A), respectively, obtained from solutions 1·5M in hydrochloric acid, are in reasonable agreement with those obtained in 0·5M-hydrochloric acid, *viz.*, $2{\cdot}1 \times 10^3$ and 1·13 (B) (Table 1). (The mercury drop weight and time were kept constant

TABLE 1. *Diffusion currents of tin in chloride–tartrate medium*

Concentration of tin = $5{\cdot}0 \times 10^{-3}$ mole/l.; 0·005% of gelatin present.

(A)	HCl, M	NH_4Cl, M	H_2T, M	i *	(B)	HCl, M	NH_4Cl, M	H_2T, M	i
	1·5	3·0	—	43·25		0·5	2·5	—	43·25
	1·5	3·0	0·2	41·63		0·5	2·5	0·2	40·50
	1·5	3·0	0·5	39·00		0·5	2·5	0·5	36·00

K (see above) = $1{\cdot}2 \times 10^3$; $m = 1{\cdot}03$. $K = 2{\cdot}1 \times 10^3$; $m = 1{\cdot}13$.

* i = Microampères at constant drop weight and time.

throughout.) Greater agreement cannot be expected in view of neglect of activity corrections and experimental limitations on the accuracy of diffusion current measurment (changes in $D^{\frac{1}{2}}$, the diffusion coefficient term of Ilkovic's diffusion current expression, are probably not significant). The values (A) are more reliable, since they were obtained under conditions more suitable for reversible-wave formation. It thus appears that the predominant complex formed in these stannic–tartrate solutions is the 1 : 1 species.

(II) *Germanium.*—(a) pH *Measurements.* Reproducible curves were obtained on titrating germanium–tartrate solutions against sodium hydroxide; the pH values did not vary within 24 hours (cf. tin series). Fig. 2 shows the existence of two end-points in the complex solution, the first representing the neutralisation of the hydrochloric acid present, and the second that of the tartaric acid. The liberation of hydrochloric acid on complex formation is indicated by comparison with the curve for non-complexed germanium. The value thus obtained by difference may be only approximate, since it assumes similar hydrolysis and aggregation characteristics in both types of solution, and experimentally, buffering made end-points difficult to identify. Approximately $3{\cdot}2 \times 10^{-4}$ mole of hydrogen ion was liberated by $1{\cdot}0 \times 10^{-4}$ mole of germanium on complex formation (Table 2). This is perhaps best explained by reactions such as

$$\begin{cases} GeCl_6^{--} + H_2T \longrightarrow GeCl_4\,(T)^{--} + 2HCl \\ GeCl_6^{--} + 2H_2T \longrightarrow GeCl_2\,(T)_2^{--} + 4HCl \end{cases}$$

TABLE 2. pH *Titrations of germanium solutions.*

$1{\cdot}0 \times 10^{-3}$ mole/l. of Ge + $4{\cdot}0 \times 10^{-3}$ mole/l. of complex-forming acid against 0·082N-NaOH.
HCl titre of blank Ge solution = 26·0 ml. of NaOH. Total solution vol. = 100 ml.

(A) Tartaric acid.
HCl titre = 30·0 ml. of NaOH.
H_2T titre = 6·0 ml. of NaOH ≡ $2{\cdot}45 \times 10^{-4}$ mole of $[H_2T]$.
HCl liberated ≡ 4·0 ml. of NaOH ≡ $3{\cdot}26 \times 10^{-4}$ mole of $[H^+]$

Since $4{\cdot}0 \times 10^{-4}$ mole of $[H_2T]$ had been added $(4{\cdot}0 - 2{\cdot}45) \times 10^{-4}$ mole was removed by complex formation = $1{\cdot}55 \times 10^{-4}$ mole of H_2T ≡ $3{\cdot}12 \times 10^{-4}$ mole of $[H^+]$.

$1{\cdot}0 \times 10^{-4}$ Ge + $4{\cdot}0 \times 10^{-4}$ $H_2T \longrightarrow$ $3{\cdot}26 \times 10^{-4}$ HCl + $2{\cdot}45 \times 10^{-4}$ H_2T (all in moles).

(B) Malic acid } Same end-point data. Titration curves more buffered the weaker the acid
(C) Succinic acid } ($K_{H_2T} > K_{H_2M} > K_{H_2Succ.}$).

the participation of a $GeCl_6^{--}$ ion being assumed for simplicity of representation. $[GeCl_{6-x}(OH)_x^{--}$ would, for example, be a more general picture of the monomeric ion]. This then correlates with the complex-forming ratios of 1 : 1 and 1 : 2 found for tin. It is noteworthy that malic and succinic acids gave essentially the same results, suggesting similar behaviour by these acids on complex-formation with germanium. The evidence is by no means independently conclusive, however.

(b) *Polarimetric measurements.* Figs. 3 and 4 show variation curves for germanium–tartrate systems in hydrochloric acid and ammoniacal media (all results were completely reproducible). In all the acid series a well-defined maximum manifests itself at the composition 1[Ge] : 1[H_2T], acidity change altering the complex concentration (indicated by activity values) negligibly.

Curvature, becoming more pronounced as the acidity decreases, suggests the existence of more than one complex species.

The ammoniacal series show that the 1 : 2 complex may be this other species. The apparent lævorotation at high germanium : tartrate ratios may be indicative of yet another complex, but it was not possible to extend the curve to a turning point, owing to precipitations occurring before measurement could be made. The simplest species would be the 2 : 1 complex.

Effects of ageing. As with tin, ageing caused an increase in rotation for the acid series, without change in the maximum position. After 3 months, the activity remained constant. In the ammoniacal solutions, precipitation occurred quite rapidly.

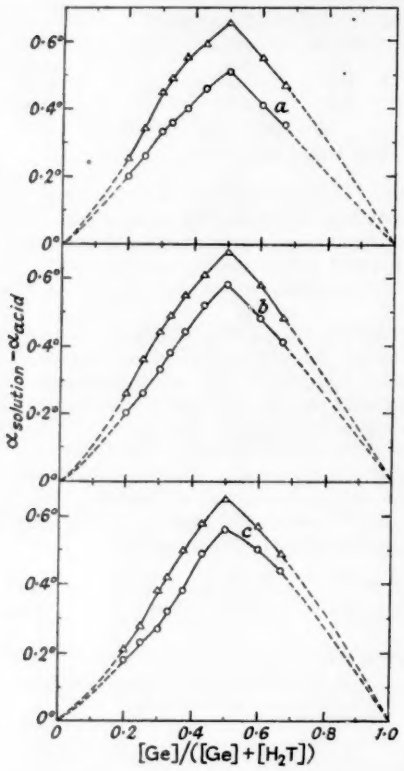
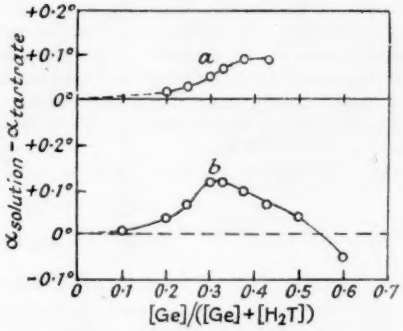


FIG. 3. *Optical activity variation curves for germanium and tartaric acid.*

○ = Fresh solutions. Δ = Aged solutions.

(*a*) Ge–H_2T, 2N in HCl. (*b*) Ge–H_2T, N in HCl. (*c*) Ge–H_2T, 0·1N in HCl.

FIG. 4. *Optical activity variation curves for germanium and tartaric acid.*



(*a*) Ge–H_2T, 0·5N in NH_4OH.
(*b*) Ge–H_2T, 0·1N in NH_4OH.

(c) *Polarographic measurements.* No wave attributable to reduction of a complex was observed in germanium–tartrate solutions under acid or alkaline conditions.

(III) *Titanium.*—(a) pH *Measurements.* A preliminary "static" titration of a solution containing titanium and tartaric acid in the ratio 3 : 4 gave non-reproducible results, although

TABLE 3. pH *Titrations of titanium solutions.*

$1{\cdot}0 \times 10^{-3}$ mole/l. of Ti + $4{\cdot}0 \times 10^{-3}$ mole/l. of complex-forming acid against 0·05N-NaOH.
HCl titre of blank Ti solution = 20·5 ml. of NaOH. Total solution vol. = 100 ml.

(A) Tartaric acid.

HCl titre = 26·5 ml. of NaOH.
H_2T titre = 11·5 ml. of NaOH ≡ $2{\cdot}6 \times 10^{-4}$ mole of $[H_2T]$.
HCl liberated = 6·0 ml. of NaOH ≡ 3×10^{-4} mole of $[H^+]$.

Since $4{\cdot}0 \times 10^{-4}$ mole of $[H_2T]$ had been added, $(4{\cdot}0 - 2{\cdot}6) \times 10^{-4}$ mole was removed by complex formation = $1{\cdot}4 \times 10^{-4}$ mole of $H_2T \equiv 2{\cdot}8 \times 10^{-4}$ mole of $[H^+]$.

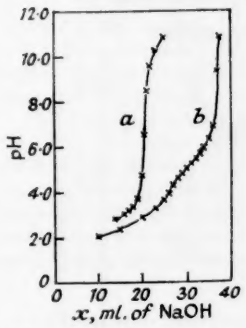
$$1{\cdot}0 \times 10^{-4}\ \text{Ti} + 4{\cdot}0 \times 10^{-4}\ H_2T \longrightarrow 3{\cdot}0 \times 10^{-4}\ \text{HCl} + 2{\cdot}6 \times 10^{-4}\ H_2T \text{ (all in moles)}.$$

(B) Malic acid } Same end-point data. Titration curves more buffered the weaker the acid.
(C) Succinic acid }

the pH did not vary greatly with time. However, at a higher tartaric acid concentration (ratio = 1[Ti] : 4[H_2T]), reasonable reproducibility was achieved, the curve giving end-point data (Table 3 and Fig. 5) similar to those for germanium; again, malic and succinic acids behaved similarly to tartaric acid. No observable variation in pH had occurred after a period of two months.

The similarity in behaviour of titanium and germanium suggests a similarity in the complex-forming processes. Bearing in mind the reservations mentioned in (II), it may be inferred that 1 : 1 and 1 : 2 complex formation occurs between titanium and tartaric, malic, or succinic acids.

FIG. 5. pH *Titration curves of titanium.*



x Ml. of 0·05N-NaOH against 1×10^{-4} mole of Ti (in 10 ml.) +

(*a*) (90 − x) ml. of H_2O.
(*b*) 20 ml. of 0·02M-H_2T + (70 − x) ml. of H_2O.

FIG. 6. *Optical activity variation curves for titanium and tartaric acid.*

○ = Measurements after 3 minutes.

(*a*) Ti–H_2T, N in NH_4OH.
(*b*) Ti–H_2T, 0·5N in NH_4OH.
(*c*) Ti–H_2T, 0·1N in NH_4OH.

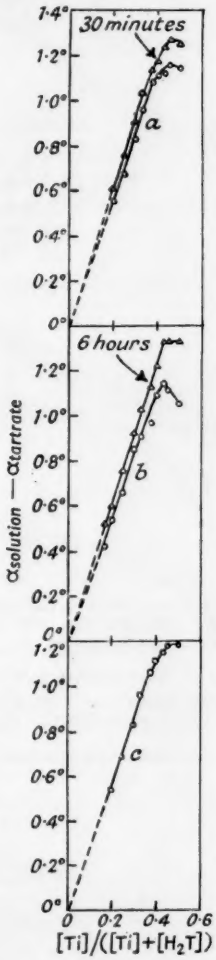
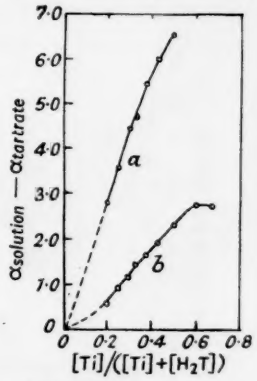


FIG. 7. *Optical activity variation curves for titanium and tartaric acid.*



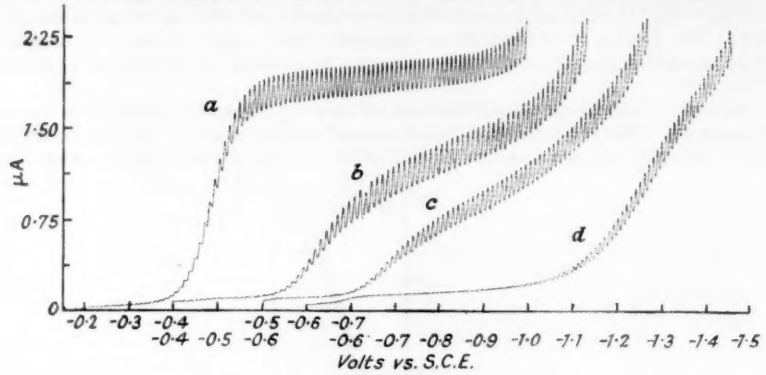
(*a*) Ti–H_2T, 0·5N in HCl.
(*b*) Ti–H_2T, N in HCl.

(b) *Polarimetric measurements.* Variation curves for the optical activity of ammoniacal dilute titanium–tartrate systems are shown in Fig. 6; rapid precipitation prevented measurements from being made at [Ti]/([Ti] + [H_2T]) ratios greater than 0·50. In acid medium, good reproducibility was not obtained, owing to low activity values and sensitivity to slight changes in acidity.

Precipitation also restricted measurements at the more concentrated level. Here, as in the dilute series, definite maxima are not evident (Fig. 7).

Effects of ageing. As in (I) and (II), ageing brought about a rise in the activity (Fig. 6). Basic solids were precipitated, the time before deposition decreasing as the [Ti] : [H_2T] ratio

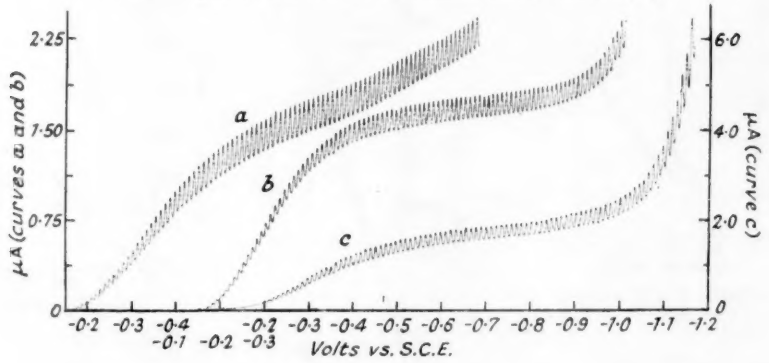
FIG. 8. *Effect of* pH *on reduction wave of titanium*(IV) *in tartaric acid solution.*



$1{\cdot}0 \times 10^{-4}$ mole of Ti/l.; 0·2M in H_2T.

(*a*) pH = 1·22; $E_{\frac{1}{2}} = -0{\cdot}48$ v. (*b*) pH = 2·37; $E_{\frac{1}{2}}$ indeterminate.
(*c*) pH = 2·76; $E_{\frac{1}{2}}$ indeterminate. (*d*) pH = 3·99; $E_{\frac{1}{2}}$ indeterminate.

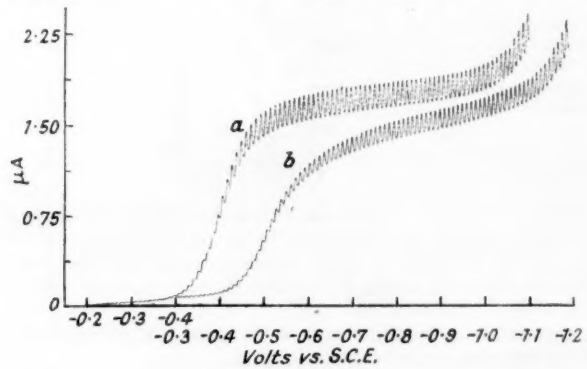
FIG. 9. *Effect of acid strength on reduction wave of titanium*(IV).



$1{\cdot}0 \times 10^{-3}$ mole/l.

(*a*) M in HCl, 0·2M in H_2T; $E_{\frac{1}{2}}$ indeterminate. (*b*) M in HCl, 0·5M in H_2T; $E_{\frac{1}{2}} \sim -0{\cdot}31$ v.
(*c*) M in HCl, 3M in NH_4Cl; $E_{\frac{1}{2}}$ indeterminate.

FIG. 10. *Effect of tartaric acid concentration on reduction wave of titanium*(IV) *in tartaric acid.*



$1{\cdot}0 \times 10^{-3}$ mole/l.

(*a*) 0·5M in H_2T; $E_{\frac{1}{2}} = -0{\cdot}51$ v. (*b*) M in H_2T; $E_{\frac{1}{2}} \sim -0{\cdot}52$ v.

increased. In the acid concentrated solutions, salting out occurred in all solutions, without prior activity increase.

Apparently the titanium–tartrate complexes exist in sluggish equilibrium with each other. The indications are that a 2 : 1 complex exists in acid concentrated solutions, together with others which may be the 1 : 1 and 1 : 2 species. The presence of these two would account for the maximum at 3 : 4 in the ammoniacal series. Condensed species (such as the 2 : 3 complex suggested by Caglioti) are highly probable, also.

(c) *Polarographic measurements.* Although it has frequently been demonstrated that titanium in an excess of tartaric acid solution gives a reversible reduction wave (Pecsok, *J. Amer. Chem. Soc.*, 1951, **73**, 1304; Strubl, *Coll. Czech. Chem. Comm.*, 1938, **10**, 475; Caglioti and Sartori, *loc. cit.*), the effect of varying the conditions has not been greatly studied. Various constraints were therefore applied :

(i) Effect of pH. The polarograms of $1{\cdot}0 \times 10^{-3}$M-titanium in 0·2M-tartaric acid at varying pH (controlled by addition of sodium hydroxide) are shown in Fig. 8. Increasing the pH is shown to destroy rapidly the reversible nature of the waves, and reduction occurs at more negative potentials. Above pH ~4, no wave due to titanium is obtained. These are effects similar to those observed for titanium–oxalic acid solutions (Pecsok, *loc cit.*). Apparently as the pH increases, hydrolysis and aggregation render reduction more difficult.

(ii) Effect of acid strength. When the solution is made M in hydrochloric acid, the wave became less reversible than at pH ~1, shifting to more positive potential values (Fig. 9, *a*). Increasing the tartaric acid content from 0·2 to 1·0M somewhat counteracts this effect (Fig. 9, *b*). It is probable that, as the hydrochloric acid content is increased relative to that of the tartaric acid, the competing effect of the strong acid dissociates the tartrate complex, and the wave assumes a shape approaching that given by titanium in chloride medium (Fig. 9, *c*).

(iii) Effect of tartaric acid concentration. In Fig. 10 it is demonstrated that increasing the tartaric acid concentration causes the wave to become less reversible, and the half-wave potential is shifted to more negative values (see also Fig. 8, *a*). The tendency to irreversibility is due either to large quantitites of tartaric acid decreasing the reduction rate at the dropping electrode (large quantities of neutral salts sometimes exhibit this effect : see Cambridge Instrument Co. polarograph manual) or to the formation of a second complex in appreciable quantities, both species being reduced at similar potentials.

Discussion

The evidence here presented points very strongly to 1 : 1 and 1 : 2 complex formation of metal : tartrate for the three elements examined, and similar behaviour is inferred with malic or succinic acids as complex-forming agents. There is no doubt, however, that other complexes exist under different conditions, polynuclear species included.

The extreme difficulty of identifying each ionic species is clearly seen when it is remembered that, except in very strongly acid solutions, considerable hydrolysis takes place. Although a 1 : 1 or 1 : 2 complex may be identifiable, the number of hydroxyl groups in the ion varies. Unless the concentrations of each individual species are known, dissociation constants cannot be calculated; failure to appreciate this has vitiated some earlier work (cf. Caglioti, p. 990). The polarographic measurements show clearly the marked effect of pH change. It is also to be borne in mind that hydrolysis here precedes aggregation, which may be considerable, thereby further complicating the analysis.

The ageing phenomena noted are consistent with a slow aggregation process following rapid hydrolysis, by means of intermolecular condensation. This may be achieved in a variety of ways, the species growing in size to become micellar or colloidal, eventually to be precipitated if conditions permit the process to continue. Such tendencies would be favoured by low acidity (or alkaline conditions), high metal concentration relative to complex-forming agent concentration (or high concentration in general), and presence of salting-out electrolytes. These have all been demonstrated.

I thank Mr. H. Holness, under whose supervision this work was carried out, for his guidance and criticisms, and also the Department of Scientific and Industrial Research for a maintenance grant.

South-West Essex Technical College, Walthamstow, London, E.17.
[Present address : Technical University of Denmark,
Sölvgade 83, Copenhagen K.]

[*Received, October 6th*, 1953.]

Reactions of 4-Thionchromones with Amino-compounds, and with Methyl Iodide.

By Wilson Baker, G. G. Clarke, and J. B. Harborne.

[Reprint Order No. 4841.]

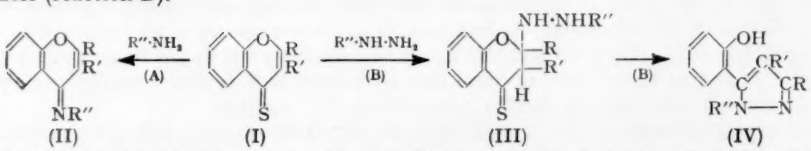
The study of the behaviour of 4-thionchromones with primary aliphatic amines, certain carbonyl reagents, and methyl iodide has been extended. Reagents containing primary amino-groups usually give derivatives of either chromone imine (II) or *o*-hydroxyphenylpyrazole (IV).

The reaction of 4-thionchromones (*e.g.*, I) with primary amino-compounds has been but little studied (see Campaigne, *Chem. Reviews*, 1946, **39**, 64), and we now record an extension of our previous investigation (see Baker, Harborne, and Ollis, *J.*, 1952, **1303**, where references to earlier work are included).

The following 4-thion-chromones and -flavones have been prepared from the corresponding chromones and flavones by reaction with phosphorus pentasulphide: 2-ethoxycarbonyl, 2-2′-furyl-, 2-methyl-3-phenyl-, and 2 : 3-diphenyl-4-thionchromones, 4-thion*iso*flavone, and 3-hydroxy-, 7-methoxy-, 4′-methoxy-, 5 : 7-dimethoxy-, and 3-methyl-4-thionflavone. The behaviour of these compounds with benzylamine, hydrazine, phenylhydrazine, and methyl iodide has been investigated. With the reagents containing primary amino-groups, two types of reaction are encountered.

Reaction (A) is simple condensation with elimination of hydrogen sulphide; it occurs with nearly all 4-thionflavones (I; R = Ph, R′ = H) to give derivatives of 4-iminoflavone, *e.g.*, flavone benzylimine, hydrazone, and phenylhydrazone (II; R = Ph, R′ = H, R″ = Ph·CH_2, NH_2, and Ph·NH). The same reactivity of the thione group is observed if the phenyl group in position 2 is replaced by an α-furyl group (I; R = 2-furyl, R′ = H). A 4-thionflavone having a methyl, phenyl, or hydroxyl group in position 3 (I; R = Ph, R′ = Me, Ph, or OH) is either inert or undergoes the second type of reaction.

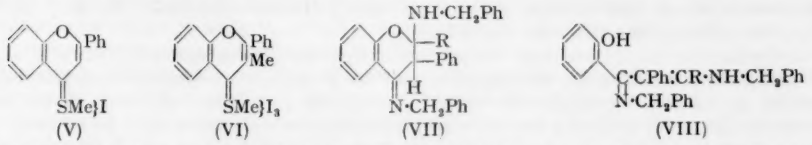
Reaction (B) is exemplified by 4-thionchromone (I; R = R′ = H), 2-methyl-4-thionchromone (I; R = Me, R′ = H), or 5 : 7-dimethoxy-4-thionflavone, which undergo opening of the pyrone ring with hydrazine or with phenylhydrazine to give colourless, phenolic pyrazoles (IV). The reaction is probably initiated by attack on the cationoid carbon atom 2 by the anionoid NH_2-group of the hydrazine. The resulting addition product (III) must then rearrange to the phenolic open-chain hydrazone, and subsequently cyclise with loss of hydrogen sulphide to give the pyrazole (IV) (see Baker, Harborne, and Ollis, *loc. cit.*; Baker and Butt, *J.*, 1949, 2144). 7-Methoxy-4-thionflavone reacts with hydrazine to give 7-methoxyflavone hydrazone (reaction A), and a trace of the related pyrazole (reaction B).



2-Methyl-4-thionchromone does not react with benzylamine in boiling alcoholic solution. The most sensitive reagent for distinguishing between the two types of 4-thionchromone is hydrazine under mild conditions which gives either a bright yellow chromone hydrazone (II; R″ = NH_2) (reaction A), or a colourless pyrazole (IV; R″ = H) (reaction B). Under vigorous conditions the product is in all cases the *o*-hydroxyphenylpyrazole, since the chromone hydrazones are converted into the isomeric phenolic pyrazoles when boiled with ethanolic hydrazine.

Methyl iodide reacts rapidly with 4-thionflavones to give methiodides (as V) which are hydrolysed by boiling water to flavones. 2-2′-Furyl-4-thionchromone reacts similarly, but 3-phenyl- and 3-hydroxy-4-thionflavone do not react. 2-Methyl-, 2 : 3-dimethyl-, 2-methyl-3-phenyl-, and 3-phenyl-4-thionchromone give unstable methiodides which are hydrolysed rapidly on exposure to air with loss of methanethiol.

A somewhat different reaction is shown by 4-thionchromone, 3-methyl-4-thionflavone, and 2-ethoxycarbonyl-4-thionchromone, which with excess of methyl iodide at room temperature give methotri-iodides (*e.g.*, VI) in *ca.* 20% yield. The extra iodine doubtless arises by the photo-decomposition of methyl iodide; if free iodine is added to the mixture the yield of methotri-iodide is quantitative. Although periodides are well known (see



(V) (VI) (VII) (VIII)

"The Chemical Elements and their Compounds," Sidgwick, Oxford Univ. Press, 1950, p. 1194), their formation under these conditions does not appear to have been observed previously.

4-Thion*iso*flavone and 2 : 3-diphenyl-4-thionchromone each react with two molecules of benzylamine to yield products, formulated as (VII; R = H and Ph respectively), which are non-phenolic and non-fluorescent. The only alternative structures (VIII; R = H or Ph) represent compounds which would be phenolic and strongly fluorescent (cf. compounds such as 2-β-benzylaminocinnamoylphenol; Baker, Harborne, and Ollis, *J.*, 1952, 1294). Compounds (VII) doubtless arise by initial addition of benzylamine to the 2 : 3-double bond of the chromone nucleus, followed by condensation of the second molecule of benzylamine with the thione group.

Attempts have been made to rationalise the foregoing experimental facts, but satisfactory explanations cannot be advanced in the present state of our knowledge.

Note on Flavone Benzylimine Methiodide.—A compound, m. p. 266°, was prepared by heating flavone benzylimine with methanolic methyl iodide, and was described as flavone benzylimine methiodide (Baker, Harborne, and Ollis, *J.*, 1952, 1294). Attention was, however, drawn to the fact that hydrolysis gave flavone and benzylamine in place of the expected *N*-methylbenzylamine. Re-investigation of this substance has shown that it is flavone benzylimine hydriodide, and that it can be prepared quantitatively from flavone benzylimine and hydriodic acid. The true flavone benzylimine methiodide, m. p. 210—212°, has been prepared from flavone benzylimine and methyl iodide at room temperature. We have noticed (unpublished observations) that the benzylimines of xanthone and of coumarin also form hydriodides and not methiodides when heated with methanolic methyl iodide, and two other cases have been reported amongst the alkaloids (see Barger, Madinaveitia, and Streuli, *J.*, 1939, 510; Moore, *J.*, 1911, **99**, 1231).

Experimental

Preparation of 4-Thionchromones.—These compounds were prepared by heating the chromones with pure phosphorus pentasulphide in benzene, toluene, or xylene for 2—4 hr. (Baker, Harborne, and Ollis, *J.*, 1952, 1303), and crystallised from ethanol or light petroleum. The yields are given in parentheses.

2-2′-Furylchromone (Ollis and Weight, *J.*, 1952, 3826) gave *2-2′-furyl-4-thionchromone*, thick, purple needles, m. p. 108° (40%) (Found: C, 67·8; H, 3·7; S, 14·3. $C_{13}H_8O_2S$ requires C, 68·4; H, 3·5; S, 14·0%).

2-Ethoxycarbonylchromone (Schmutz *et al.*, *Helv. Chim. Acta*, 1951, **34**, 767) gave 2-ethoxycarbonyl-4-thionchromone, deep green prisms, which appeared purple in bulk, m. p. 101—103° (70%) (Found: C, 61·5; H, 4·3; S, 13·6. Calc. for $C_{12}H_{10}O_3S$: C, 61·5; H, 4·3; S, 13·7%). Schmutz *et al.* record m. p. 100—101°.

4′-Methoxyflavone gave *4′-methoxy-4-thionflavone*, red needles, m. p. 137° (74%) (Found: C, 71·4; H, 4·4; S, 11·8. $C_{16}H_{12}O_2S$ requires C, 71·6; H, 4·5; S, 12·0%).

7-Methoxyflavone was prepared (66%) by the method of Virkar and Shah (*Chem. Abs.*, 1943, **37**, 2375), except that in the Baker–Venkataraman rearrangement of 2-benzoyloxy-4-methoxyacetophenone, powdered potassium hydroxide in pyridine was used in preference to sodium in benzene. *7-Methoxy-4-thionflavone* formed large red or small orange needles, m. p. 134—136° (53%) (Found: C, 71·9; H, 4·0; S, 11·85. $C_{16}H_{12}O_2S$ requires C, 71·6; H, 4·5; S, 11·95%).

In the preparation of 5 : 7-dimethoxyflavone (Baker, Harborne, and Ollis, *J.*, 1952, 1294) the yield in the Baker–Venkataraman rearrangement was increased to 88% by allowing the solution of ester in pyridine and potassium hydroxide to stand for 3 days at room temperature. 5 : 7-*Dimethoxy*-4-*thionflavone* formed dark green prisms, m. p. 184° (Found: C, 68·8; H, 4·8; S, 10·7. $C_{17}H_{14}O_3S$ requires C, 68·4; H, 4·7; S, 10·7%).

2-Methyl*iso*flavone (Chadha, Mahal, and Venkataraman, *J.*, 1933, 1461) gave 2-*methyl*-4-*thioniso*flavone, bright red needles, m. p. 134° (54%) (Found: C, 76·3; H, 4·5; S, 13·1. $C_{16}H_{12}OS$ requires C, 76·2; H, 4·8; S, 12·7%).

3-Methylflavone is best prepared by the Allan–Robinson fusion method (Dunne *et al.*, *J.*, 1950, 1258), but, contrary to the experience of these authors, *o*-benzoyloxypropiophenone underwent the Baker–Venkataraman rearrangement, to give, after draining of the crude product on a tile, a 4% yield of 1-*benzoyl*-1-*o*-*hydroxybenzoylethane*, colourless plates, m. p. 112° (Found: C, 75·1; H, 5·1. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·5%), which gave a deep red colour with ferric chloride. 3-*Methyl*-4-*thionflavone* formed purple plates, m. p. 128—129° (55%) (Found: C, 76·4; H, 5·2; S, 11·6. $C_{16}H_{12}OS$ requires C, 76·2; H, 4·8; S, 12·7%).

*iso*Flavone (Joshi and Venkataraman, *J.*, 1934, 513) gave 4-*thioniso*flavone, thin, slate-coloured plates or thick, purple plates, m. p. 94° (63%) (Found: C, 75·9; H, 4·1. $C_{15}H_{10}OS$ requires C, 75·6; H, 4·2%). Solutions of 4-thion*iso*flavone are sky-blue in light petroleum and violet in ethanol.

2 : 3-Diphenylchromone (Chadha, Mahal, and Venkataraman, *loc. cit.*) gave 2 : 3-*diphenyl*-4-*thionchromone*, deep purple plates, m. p. 175° (69%) (Found: C, 79·5; H, 4·3; S, 10·0. $C_{21}H_{14}OS$ requires C, 80·2; H, 4·5; S, 10·2%).

Flavonol (Algar and Flynn, *Proc. Roy. Irish Acad.*, 1934, **42**, *B*, 1) gave 4-*thionflavonol*, red needles, m. p. 80—82° (55%) (Found: C, 70·9; H, 3·9. $C_{15}H_{10}O_2S$ requires C, 70·8; H, 3·9%). It gave an intense green colour with ferric chloride solution.

Reaction of 4-*Thionchromones with Benzylamine*.—The 4-thionchromones were heated with excess of benzylamine (*ca.* 2 equivs.) in ethanol for 1—2 hr. and, if reaction occurred, hydrogen sulphide was evolved and the deep colour of the solution faded. The product was then isolated by pouring the solution into water, and crystallised from ethanol. Except for 2-ethoxycarbonyl-4-thionchromone and 4-thionchromone, which were decomposed by this treatment, only the four thiones mentioned below and 4-thionflavone reacted with benzylamine.

2-2′-Furyl-4-thionchromone gave 2-2′-furylchromone benzylimine in 72% yield, colourless needles, m. p. 120—122°, alone and when mixed with an authentic specimen (Baker, Harborne, and Ollis, *J.*, 1952, 1301). 4′-Methoxy-4-thionflavone gave 4′-methoxyflavone benzylimine in 71% yield, colourless needles, m. p. and mixed m. p. 134·5—135° (*idem*, *ibid.*, p. 1300). 4-Thion-*iso*flavone gave the benzylimine (VII; R = H) in 80% yield, thick yellow plates, m. p. 109—110·5° (Found: C, 82·8; H, 6·1; N, 6·6. $C_{29}H_{26}ON_2$ requires C, 83·2; H, 6·3; N, 6·7%). 2 : 3-Diphenyl-4-thionchromone, when heated with benzylamine in ethanol for 12 hr., gave the *benzylimine* (VII; R = Ph) in 52% yield, as irregular, yellow prisms, m. p. 154—155° (Found: C, 85·0; H, 5·7; N, 6·0. $C_{35}H_{30}ON_2$ requires C, 85·0; H, 6·1; N, 5·7%).

Reaction of 4-*Thionchromones with Hydrazine*.—Hydrazine hydrate was added dropwise to a solution of the thionchromone in warm ethanol, until the deep colour of the solution faded to pale yellow or the solution became colourless, and hydrogen sulphide was liberated. After ½ hr., the product, either a chromone hydrazone or an *o*-hydroxyphenylpyrazole, was isolated by addition of water, and purified by crystallisation from a suitable solvent. Yields are given in parentheses.

The chromone hydrazones are bright yellow, insoluble in 2N-sodium hydroxide, and give no colour with aqueous-alcoholic ferric chloride. Their ultra-violet absorption curves (cf. flavone hydrazone) are very different from those of the *o*-hydroxyphenylpyrazoles.

Flavone hydrazone [light absorption in ethanol, $\lambda_{max.}$ (mμ) (log ε): 239 (4·32); 282 (4·22); 338 (4·13)] has been prepared before (Baker, Harborne, and Ollis, *loc. cit.*, p. 1306), but the following three compounds are new. 2-2′-*Furylchromone hydrazone*, bright yellow needles, m. p. 139—140°, from aqueous methanol (87%) (Found: C, 69·15; H, 4·5; N, 12·6. $C_{13}H_{10}O_2N_2$ requires C, 69·0; H, 4·4; N, 12·4%). 4′-*Methoxyflavone hydrazone*, bright yellow needles, m. p. 169°, from benzene (69%) (Found: C, 71·6; H, 5·2; N, 10·5. $C_{16}H_{14}O_2N_2$ requires C, 72·15; H, 5·3; N, 10·5%). 7-*Methoxyflavone hydrazone* crystallises from aqueous methanol as yellow solvated needles, m. p. 84—94° (variable) [Found, after drying in *vacuo* at 56° over $Mg(ClO_4)_2$: C, 71·6; H, 5·3; N, 10·6. $C_{16}H_{14}O_2N_2$ requires C, 72·2; H, 5·3; N, 10·5%]. Material, which had been purified by chromatography in benzene solution on alumina in order to remove traces of the isomeric *o*-hydroxyphenylpyrazole, retained benzene of crystal-

lisation even after subsequent crystallisation from cold aqueous methanol. The *benzene* complex formed deep yellow needles, m. p. 118—120° (Found: C, 74·4, 74·4; H, 5·9, 5·8; N, 9·3, 8·9. $C_{16}H_{14}O_2N_2,\frac{1}{2}C_6H_6$ requires C, 74·7; H, 5·6; N, 9·2%). The N-*acetyl* derivative separated from dioxan as pale-green needles, m. p. 271—273° (Found: C, 69·8; H, 5·2; N, 8·9. $C_{18}H_{16}O_3N_2$ requires C, 70·1; H, 5·2; N, 9·1%).

When boiled with ethanolic hydrazine for 2—3 hr., these chromone hydrazones are isomerised to the corresponding *o*-hydroxyphenylpyrazoles. Alternatively, if the reaction of the thionchromone with hydrazine is carried out under more vigorous conditions, the chief product is the pyrazole. For example, 4′-methoxy-4-thionflavone was heated under reflux for 1 hr. with ethanolic hydrazine hydrate, and the cold solution was poured into N-sodium hydroxide. Ether-extraction gave an 8% yield of 4′-methoxyflavone hydrazone, m. p. and mixed m. p. 168—169°. Acidification of the aqueous layer gave 3(5)-o-*hydroxyphenyl*-5(3)-p-*methoxyphenylpyrazole*, colourless plates, m. p. 139—140°, from methanol (Found: C, 72·3; H, 5·3; N, 10·3. $C_{16}H_{14}O_2N_2$ requires C, 72·15; H, 5·3; N, 10·5%). This pyrazole gave an intense purple-green colour with alcoholic ferric chloride. The *o*-hydroxyphenylpyrazoles are colourless, soluble in 2N-sodium hydroxide, and give intense colours in alcoholic solution with aqueous ferric chloride, and characteristic absorption maxima in ultra-violet light (see *idem*, *loc. cit.*, for a table of ultra-violet spectral data, and compare with the values given below).

The pyrazoles formed from thionchromone and its 2-methyl and 2 : 3-dimethyl derivatives have been described in the earlier paper. The following five are new, and all gave an intense green colour with ferric chloride, except for 3(5)-*o*-hydroxyphenyl-4-phenylpyrazole, which gave a blue colour.

5 : 7-Dimethoxy-4-thionflavone gave 3(5)-(2-*hydroxy*-4 : 6-*dimethoxyphenyl*)-5(3)-*phenylpyrazole*, prisms, m. p. 116—117° (from methanol) (81%) (Found: C, 67·8; H, 5·2; N, 9·3. $C_{17}H_{16}O_3N_2$ requires C, 68·9; H, 5·4; N, 9·5%).

2-Methyl-3-phenyl-4-thionchromone gave 3(5)-o-*hydroxyphenyl*-5(3)-*methyl*-4-*phenylpyrazole*, needles, m. p. 180° (from dilute methanol) (83%) (Found: C, 76·6; H, 5·6; N, 11·0. $C_{16}H_{14}ON_2$ requires C, 76·8; H, 5·6; N, 11·2%).

3-Methyl-2-phenyl-4-thionchromone gave 3(5)-o-*hydroxyphenyl*-4-*methyl*-5(3)-*phenylpyrazole*, needles, m. p. 138—140° (from carbon tetrachloride) (70%) (Found: C, 76·3; H, 5·7; N, 11·1. $C_{16}H_{14}ON_2$ requires C, 76·8; H, 5·6; N, 11·2%). Light absorption in ethanol, $\lambda_{max.}$ (mμ) (log ε): 214 (4·66); 249 (4·60); 288 (4·12).

4-Thion*iso*flavone gave 3(5)-o-*hydroxyphenyl*-4-*phenylpyrazole*, solvated needles, m. p. after drying 114—116° [from chloroform–light petroleum (b. p. 40—60°)] (90%) (Found, in material dried at 78° in *vacuo*: C, 76·2; H, 5·0; N, 11·9. $C_{15}H_{12}ON_2$ requires C, 76·2; H, 5·1; N, 11·9%). Light absorption in ethanol: intense absorption, max. at *ca.* 205; $\lambda_{max.}$ (mμ) (log ε): 254 (4·04); 293 (3·74).

2 : 3-Diphenyl-4-thionchromone gave 3(5)-o-*hydroxyphenyl*-4 : 5(3 : 4)-*diphenylpyrazole*, needles, m. p. 230—231° (decomp.) [from light petroleum (b. p. 100—120°)] (85%) (Found: C, 80·9; H, 5·1; N, 9·0. $C_{21}H_{16}ON_2$ requires C, 80·7; H, 5·2; N, 9·0%).

Reaction of 4-*Thionchromones with Phenylhydrazine.*—The reaction of thionchromones with phenylhydrazine (1·5—2 equivs.) in ethanol is much slower than with hydrazine, and is carried out at 100° for 2—3 hr. or longer. In the absence of alkali, only 4-thionflavone, 2-2′-furyl-4-thionchromone, and 4-thionchromone react; with a trace of dilute alkali present, 2-methyl-, 2 : 3-dimethyl-, and 2-methyl-3-phenyl-4-thionchromones react. The other thionchromones tested were heated for 2—6 hr. with ethanolic phenylhydrazine, and recovered unchanged. The new products only are described below; the others are described in the earlier paper (*loc. cit.*).

2-2′-*Furylchromone phenylhydrazone* was obtained as deep yellow needles, m. p. 156—158°, in 23% yield, by heating the corresponding thione with ethanolic phenylhydrazine overnight (Found: C, 75·5; H, 4·4; N, 9·2. $C_{19}H_{14}O_2N_2$ requires C, 75·5; H, 4·7; N, 9·3%).

5-o-*Hydroxyphenyl*-1-*phenylpyrazole* was produced in 89% yield by warming 4-thionchromone with phenylhydrazine in ethanol for 1 hr. It separated from aqueous ethanol as colourless needles, m. p. 105—106° (Found: C, 76·7; H, 5·1; N, 11·9. $C_{15}H_{12}ON_2$ requires C, 76·2; H, 5·1; N, 11·9%). Light absorption in ethanol: intense absorption, max. at *ca.* 205; $\lambda_{max.}$ (mμ) (log ε): 286 (4·28); 303 (4·21).

3(5)-o-*Hydroxyphenyl*-5(3)-*methyl*-1 : 4-*diphenylpyrazole* was obtained by heating 2-methyl-3-phenyl-4-thionchromone (500 mg.), phenylhydrazine (2 c.c.), 5N-sodium hydroxide (3 drops), and *n*-propanol (20 c.c.) at 100° for 3 hr. and then acidifying the mixture. The pyrazole (505 mg., 78%) separated from aqueous methanol (charcoal) as colourless prisms, m. p. 219—220° (Found: C, 80·2; H, 5·4; N, 8·4. $C_{22}H_{18}ON_2$ requires C, 80·95; H, 5·6; N, 8·6%).

Reaction of 4-Thionchromones with Methyl Iodide.—Except for 4-thionflavonol and 2 : 3-diphenyl-4-thionchromone, all the thiones examined readily react with methyl iodide at room temperature, to give methiodides of varying stability. To avoid the possibility of decomposition during crystallisation, most of the products were analysed directly without further purification.

(*a*) *Formation of stable methiodides.* It was found that four of the thionchromones formed stable methiodides when dissolved in methyl iodide. The products crystallised from the solution, in some cases within a few minutes, and were collected after 24 hr., washed with ether and dried.

2-2′-Furyl-4-thionchromone methiodide, maroon needles, m. p. 195° (92%) (Found : C, 45·0; H, 2·9; S, 9·3. $C_{14}H_{11}O_2SI$ requires C, 45·4; H, 3·0; S, 8·7%). *4′-Methoxy-4-thionflavone methiodide*, red needles, m. p. 206—207° (decomp.) (83%) (Found : C, 49·5; H, 3·8; S, 5·8; I, 29·6. $C_{17}H_{15}O_2SI$ requires C, 49·8; H, 3·7; S, 7·8; I, 30·9%). *7-Methoxy-4-thionflavone methiodide*, orange needles, m. p. 210—212° (decomp.) (100%) (Found : C, 50·4; H, 3·6; S, 6·9. $C_{17}H_{15}O_2SI$ requires C, 49·8; H, 3·7; S, 7·8%). *5 : 7-Dimethoxy-4-thionflavone methiodide* maroon cubes, m. p. 214° (decomp.) (Found : C, 49·35; H, 4·2; S, 6·8. $C_{18}H_{17}O_3SI$ requires C, 49·1; H, 3·9; S, 7·3%). These four methiodides were hydrolysed by boiling water in 10—20 min. to the corresponding chromones in high yield (cf. conversion of 4-thionflavone methiodide into flavone; *idem, ibid.*).

(*b*) *Formation of methotri-iodides.* The following 4-thionchromones form stable methotri-iodides in low yield, when set aside in methyl iodide.

When kept overnight, a solution of 2-ethoxycarbonyl-4-thionchromone (131 mg.) in methyl iodide (2 c.c.) deposited carmine needles, m. p. 166° of the methotri-iodide (35 mg., 17%) (Found : C, 25·1, 25·05; H, 2·5, 2·1; S, 4·5, 5·45. $C_{13}H_{13}O_3SI_3$ requires C, 24·8; H, 2·1; S, 5·1%).

Ether was added to a solution of 3-methyl-4-thionflavone in methyl iodide which had been kept for 24 hr., giving the *methotri-iodide* as brown needles, m. p. 99—100° (20%) (Found : C, 32·7; H, 2·6; S, 4·8. $C_{17}H_{15}OSI_3$ requires C, 31·5; H, 2·3; S, 4·9%).

A solution of 4-thionchromone (200 mg.) in methyl iodide (3·4 c.c.) deposited crystals of the *methotri-iodide* (155 mg., 23%) during 4 hr. It formed large, purple-red or small, brown needles, m. p. 148—150° (Found : C, 21·7; H, 1·8; S, 6·7; I, 66·4. $C_{10}H_9OSI_3$ requires C, 21·5; H, 1·6; S, 5·75; I, 68·2%). In a second experiment, 4-thionchromone (210 mg.), methyl iodide (10 c.c.), and iodine (310 mg.) were kept for 12 hr., and the crystals washed with ether and chloroform; the product had m. p. 148—150° (695 mg., 95%).

(*c*) *Formation of unstable methiodides.* The following four thionchromones gave unstable methiodides.

2 : 3-Dimethyl-4-thionchromone (500 mg.), chloroform (5 c.c.), and methyl iodide (5 c.c.) were kept overnight. On addition of ether, deep purple needles, m. p. 75°, separated (172 mg., 20%)]. This methiodide could not be analysed as it quickly decomposed with loss of methanethiol. 2-Methyl-4-thionchromone methiodide had similar properties.

The violet solution of 4-thion*iso*flavone (100 mg.) in methyl iodide (2 c.c.) became red during 24 hr. No solid separated on the addition of ether, but the odour of methanethiol was evident. The solution was then evaporated at 15°, and the residue crystallised from ethanol (charcoal), giving *iso*flavone, m. p. and mixed m. p. 130—131° (45 mg., 48%). Similarly 2-methyl-4-thion-*iso*flavone was converted into 2-methyl*iso*flavone.

Flavone Benzylimine Hydriodide.—The substance, m. p. 266°, previously prepared (Baker, Harborne, and Ollis, *loc. cit.*) was reanalysed (previous figures in parentheses) [Found : C, 59·6 (60·3); H, 3·7 (4·2); (N, 3·3); I, 29·2 (28·8). $C_{22}H_{17}ON,HI$ requires C, 60·1; H, 4·1; N, 3·2; I, 28·9%]. It was prepared in quantitative yield by addition of hydriodic acid (*d* 1·5) to a solution of flavone benzylimine in acetic acid.

Flavone Benzylimine Methiodide.—Flavone benzylimine (2·1 g.) in methyl iodide (20 c.c.) was left at room temperature for 4 days, and the crystalline product was collected, washed with ether, and dried. The *methiodide* (2·69 g., 88%) crystallised from acetone–ether as bright yellow needles, m. p. 210—212° (decomp.) (Found : C, 61·0; H, 4·9; N, 3·1. $C_{22}H_{17}ON,CH_3I$ requires C, 60·9; H, 4·5; N, 3·1; I, 28·0%).

The authors thank the Department of Scientific and Industrial Research for a maintenance allowance awarded to Mr. G. G. Clarke.

THE UNIVERSITY, BRISTOL. [*Received, November 27th,* 1953.]

*Constituents of the Lipids of Tubercle Bacilli. Part II.**

By J. D. CHANLEY and N. POLGAR.

[Reprint Order No. 4850.]

The lipid extracts of tubercle bacilli (human type) have been subjected to a two-step hydrolysis, and the resulting dextro- and lævo-rotatory acids studied. The dextrorotatory mixture of acids, liberated by a mild hydrolysis, is shown to exhibit αβ-unsaturation (cf. *Nature*, 1950, **166**, 693). The lævorotatory acid resulting from a more vigorous hydrolysis of the remaining mixture of the lipids is found to be saturated. Some preliminary studies pertaining to the structure of these acids are also described.

PRELIMINARY studies of the component acids of the lipids of tubercle bacilli (human type) (Part I *) resulted in the isolation of three dextrorotatory acids which, as already briefly reported (Chanley and Polgar, *Nature*, 1950, **166**, 693) showed αβ-unsaturation. Two of these acids, having $[\alpha]_D$ +11·7° and +11°, respectively, had molecular weights and optical rotations similar to those of the "phthioic acid," isolated by Anderson and his collaborators (Anderson and Chargaff, *J. Biol. Chem.*, 1929, **85**, 77; Spielman and Anderson, *ibid.*, 1936, **112**, 759) and formulated as $C_{26}H_{52}O_2$. The third acid (approximately C_{30}) having $[\alpha]_D$ +4·8°, was probably a mixture including as a major constituent the lævorotatory acid described below. These acids were isolated by a fractional crystallization of the semicarbazones and the 2 : 4-dinitrophenylsemicarbazones of their acetol esters. Although some separation of the initial mixture was achieved, the acids were obtained in too small amounts for further purification and for detailed structural studies.

In the work now described, which was carried out in 1949—1950, a simplified procedure of isolating the hydrolytic product of the lipids was employed. This was based upon the following observations. (*a*) Mild hydrolysis of the lipid extracts (obtained by Soxhlet-extraction of the bacterial cells with acetone, and then with *iso*propyl ether) liberates mixtures of the dextrorotatory acids with acids of lower molecular weight, from which the dextrorotatory acids can be easily separated by distillation of their methyl esters. (*b*) The dextrorotatory mixture of acids thus liberated is soluble in cold methanol, whereas the unhydrolysed lipids are very sparingly soluble and are thus readily separable from the former. (*c*) Further hydrolysis of the resulting methanol-insoluble lipid fraction under more vigorous conditions releases a lævorotatory acid. (*d*) Both the dextro- and the lævo-rotatory acids yield potassium salts which are sparingly soluble in water, but readily soluble in ether at ordinary temperatures, and are partly deposited from the ethereal solutions at about 10° or below.

Details of the isolation of these acids are described in the Experimental section. It should be noted that we avoided separating the lipid extracts into fat, phosphatide, and wax fractions, since mutual solubility effects usually result in considerable overlap in the composition of such fractions. At the present stage of this investigation directed, in the first instance, towards isolating the constituent acids of the lipids, it seemed preferable to hydrolyze the total lipid extracts.

The dextrorotatory acids were separated into two fractions by the solubility of their potassium salts in ether. The less soluble fraction yielded a solid acid having $[\alpha]_D$ +7·9°, n_D^{36} 1·4600, and the potassium salt which remained in the ethereal solution on cooling gave a liquid acid having $[\alpha]_D$ +10·3°, n_D^{36} 1·4655, after decolorization by chromatography over silica. It appeared that this preliminary separation might facilitate further studies.

The ultra-violet absorption of both the solid and the liquid acid ($\lambda_{max.}$ 2200 Å; log ε 3·94 and 4·04, respectively) was characteristic of an αβ-unsaturated acid. This was confirmed by the infra-red absorption spectra which showed bands at **1646** (conjugated C=C) and at **1694** cm.$^{-1}$ (conjugated CO_2H). The ultra-violet and infra-red absorption spectra of the hydrogenated products showed the absence of unsaturation.

* Part I, *Biochem. J.*, 1948, **42**, 206.

The specific rotations were considerably decreased on hydrogenation, namely, from +7·9° to +1·1° for the solid, and from +10·3° to +1·7° for the liquid acid. This already suggested the presence of an asymmetric centre near the double bond.

An early ozonization experiment on the solid acid is recorded in the Experimental section. A discussion is reserved for the following communication (Part III) where the full chemical evidence establishing the structure of the αβ-unsaturated constituent of the solid acid, now named mycolipenic acid, is given.

According to Spielman and Anderson (*loc. cit.*) "phthioic acid," isolated from the lipids of tubercle bacilli by a procedure involving hydrogenation, had $[\alpha]_D$ +12·5°. In view of the fact that the rotatory power of the dextrorotatory acids from tubercle bacilli is considerably decreased on hydrogenation, the high rotatory power given for "phthioic acid" indicates that the hydrogenation carried out by Spielman and Anderson was incomplete. This is confirmed by Cason and Sumrell's recent studies (*J. Biol. Chem.*, 1951, **192**, 405) of a specimen of "phthioic acid" originating from Anderson and his collaborators; ester-fractionation of this product resulted in a variety of fractions including αβ-unsaturated acids.

The lævorotatory acid, exhibiting $[\alpha]_D$ −8·7° on isolation through its potassium salt, was converted into the methyl ester. Distillation afforded, as the main product, an ester fraction having $[\alpha]_D$ −10·3°. This gave on alkaline hydrolysis (see below) the corresponding acid, which was found to be saturated (no change on hydrogenation over platinic oxide; no high-intensity absorption in the ultra-violet; absence of bands characteristic for unsaturation from the infra-red spectra). Titration gave a result in close agreement with the formula $C_{31}H_{62}O_2$.

The acid obtained on hydrolysis of the preceding methyl ester with aqueous ethanolic potassium hydroxide had $[\alpha]_D$ −9·2°, whereas hydrolysis by anhydrous methanolic potassium hydroxide afforded an acid having $[\alpha]_D$ −6·9°. The decrease in rotatory power in the latter reaction suggested partial racemization in respect of an asymmetric centre in the α-position to the carboxyl group, and this was confirmed by a stepwise degradation. This involved oxidation of the derived α-hydroxy-acid (obtained through the α-bromo-acid) by means of lead tetra-acetate. The product was a ketone, thus indicating the presence of one alkyl substituent at the α-carbon atom of the parent acid. Details of further degradative studies, recently reported in a preliminary note (Polgar, *Chem. and Ind.*, 1953, 353) are given in one of the following communications (Part IV).

Anderson and his collaborators have isolated from the wax fractions of human tubercle bacilli lævorotatory acids of similar composition, having $[\alpha]_D$ −6·1°, −9·5°, and −5·7°, severally (Anderson, *J. Biol. Chem.*, 1932, **97**, 639; 1938, **126**, 515; 1945, **157**, 203), of which the last, obtained by purification procedures from a crude acid having $[\alpha]_D$ −7·4°, was named "mycocerosic acid" and characterized as a *p*-bromophenacyl ester of m. p. 47—48°. The acid, $[\alpha]_D$ −6·9°, obtained in the present work on hydrolysis with anhydrous methanolic potassium hydroxide, gave a *p*-bromophenacyl ester, m. p. 31·5°. Since there is no evidence of the presence of a second, closely related lævorotatory acid, the differences in the physical properties are probably due to varying degrees in the purity of the acids, in particular owing to the presence of stereoisomerides arising from partial racemization (see above).

The physiological properties of the acids described in the present communication have been studied by Dr. J. Ungar, of Glaxo Laboratories Ltd., who kindly reported as follows:

"The acids were injected intraperitoneally into groups of four guinea-pigs (of an equal weight of 300 g.) in doses of 5, 10, and 20 mg., suspended in 0·5 c.c. of tragacanth. One guinea-pig from each group was killed at weekly intervals and examined according to the methods described earlier (Ungar, Coulthard, and Dickinson, *Brit. J. Exp. Path.*, 1948, **29**, 322).

"The dextrorotatory solid acid, injected in amounts of 20 mg., produced granulomatous lesions in the omentum and spleen, and only a few isolated nodules in the liver.

"Guinea-pigs injected with the dextrorotatory liquid acid showed a similar picture, but the granulomata were more numerous in the liver and appeared at an earlier date.

"Extensive changes were noticed after the injection of the lævorotatory acid. After

injection of 5 mg., and more so after 10 mg., the guinea-pigs have shown multiple granulomatous lesions on the omentum, spleen, liver, diaphragm, and lymph glands of the pleural cavity. Undoubtedly the most changes were observed in the guinea-pigs after the injection of the lævorotatory acid."

Experimental

Light petroleum had b. p. 40—60°. Specific rotations were measured in ether, 0·5-dm. tubes being used. Ultra-violet absorption spectra were determined in purified *cyclo*hexane.

Extraction of the Lipids.—The extractions were kindly carried out by Glaxo Laboratories Ltd., Greenford, in the following way:

Moist steam-killed cells (*M. tuberculosis*, human type, obtained from the Veterinary Laboratory, Ministry of Agriculture and Fisheries, Weybridge; 50 lb.) were extracted with acetone (30 l.) for 20 hr. in a Soxhlet apparatus. The acetone extract was then concentrated (to about 6 l.) by heat under reduced pressure, and the residual aqueous mixture extracted with *iso*propyl ether; evaporation of the extract under reduced pressure afforded the product (*A*) (145 g.).

The cells were then extracted (Soxhlet) with *iso*propyl ether (25 l.) for 20 hr. Evaporation of this extract under reduced pressure gave the product (*B*) (430 g.).

Isolation of the Dextrorotatory Mixture of Acids.—The product (*A*) (130 g.) was refluxed with a solution of potassium hydroxide (25 g.) in methanol (500 c.c.) for 5 hr. Half of the methanol was then removed by distillation, and the residual product, after dilution with water and acidification (2N-hydrochloric acid), was extracted with ether. The dried (Na_2SO_4) ethereal extract was evaporated, and the residue boiled with methanol (500 c.c.) for a few minutes. A red tar (i) separated overnight. The remaining methanolic solution was then removed by decantation and filtration, and the residual tar washed with cold methanol (50 c.c.). The combined methanol extracts on evaporation yielded the methanol-soluble substances (ii). A solution of the latter in light petroleum (400 c.c.) was extracted with a solution containing equal volumes (100 c.c. of each) of 5% aqueous potassium hydroxide and methanol and, after repetition of this procedure and re-extraction of the aqueous-methanolic layer with light petroleum (2 × 150 c.c.), the combined petroleum extracts were washed with aqueous methanol (1 : 1; 100 c.c.) (other procedures, *e.g.*, extraction of an ethereal solution with aqueous alkali, led to inseparable emulsions). Evaporation of the dried (Na_2SO_4) petroleum solution gave the non-acid material (iii) (9 g.). Dilution of the aqueous-methanolic extracts with water, followed by acidification (hydrochloric acid), and extraction with ether afforded the acids (iv) (35 g.).

The acids (iv) were converted into the methyl esters by refluxing them with methanol (250 c.c.) and sulphuric acid (8 g.) for 8 hr. After dilution with water, the product was collected with light petroleum, and the petroleum extract washed, successively, with aqueous-methanolic potassium hydroxide and aqueous methanol, then dried (Na_2SO_4) and distilled. The following fractions were collected: (*a*) b. p. <190°/0·2 mm. (23 g.); (*b*) b. p. 190—225°/0·2 mm. (5·8 g.).

Fraction (*b*) (strongly coloured) was chromatographed in light petroleum over silica (The British Drug Houses Ltd.). Elution with light petroleum yielded a pale yellow oil (5·2 g.), $[\alpha]_D^{17}$ +7·4° (*c*, 25·95); further elution with benzene gave a viscous oil (0·5 g.) which had no measurable rotation.

The extract (*B*), hydrolysed and worked up essentially as described for (*A*), afforded on distillation of the methyl esters, after a fore-run (20 g.) of lower-boiling materials, a fraction, b. p. 190—215°/0·2 mm. (1·5 g.), $[\alpha]_D^{18}$ +8·5° (*c*, 30·4).

The Solid Dextrorotatory Acid.—The above methyl ester, $[\alpha]_D^{17}$ +7·4° (5 g.), was hydrolysed by refluxing it with 5% methanolic potassium hydroxide (50 c.c.) for 5 hr. Most of the methanol was then removed by distillation, and the residue diluted with water. When the mixture was shaken with ether, the entire hydrolysed material was taken up by the ethereal extract (on washing of the ethereal layer with water, followed by the addition of some methanol, the potassium salts were found to pass partly into the aqueous phase from which they were precipitated by potassium ions, *e.g.*, by the addition of potassium hydroxide). Cooling the ethereal solution to about 10° or below precipitated a part of the potassium salts and this property was utilized for separating the potassium salts into two fractions by the following procedure.

The above ethereal extract was shaken with dilute hydrochloric acid, dried (Na_2SO_4), and

evaporated. The residual acidic material was converted into the potassium salts by the addition of the calculated amount of 5% methanolic potassium hydroxide; the methanol was then removed under reduced pressure. To the residue (dried in a desiccator) ether (50 c.c.) was added, and the solution evaporated on a steam-bath under reduced pressure. The remaining dry potassium salts were dissolved in ether (100 c.c.) by heat under reflux, and the solution was set aside at 0° overnight. The precipitated potassium salts were filtered off by gravity, washed with ice-cold ether, and then dissolved in warm ether (50 c.c.). This solution was kept at 0° for 3 hr.; the precipitated potassium salts were then collected as described above and converted into the free acids by shaking them with ether and dilute hydrochloric acid. The product (2·6 g.) was a solid, having $[\alpha]_D^{20}$ +7·9° (*c*, 25·2), n_D^{36} 1·4600, $\lambda_{max.}$ 2200 Å (log ε 3·94) (Found: C, 78·8; H, 12·5. Calc. for $C_{27}H_{52}O_2$: C, 79·4; H, 12·75%).

The Liquid Dextrorotatory Acid.—The combined ethereal mother-liquors from the potassium salts isolated according to the preceding section were evaporated, and the residue was shaken with ether and dilute hydrochloric acid. Evaporation of the dried (Na_2SO_4) ethereal extract gave a viscous liquid (1·9 g.). This was passed in light petroleum (30 c.c.) through a column of silica (10 × 1 cm.), made up with the same solvent. Elution with light petroleum and evaporation of the solvent gave a pale yellow oil (1·3 g.), b. p. 192—197° (bath)/0·01 mm., $[\alpha]_D^{16}$ +10·3° (*c*, 25·4), n_D^{36} 1·4655, $\lambda_{max.}$ 2200 Å (log ε 4·04) (Found: C, 79·2; H, 12·8%).

Hydrogenation of the Solid Dextrorotatory Acid.—A solution of the acid (0·5 g.) in glacial acetic acid (50 c.c.) was shaken under hydrogen (2 atm.) in the presence of platinic oxide (0·1 g.) at room temperature overnight. The filtered solution was distilled, to give the saturated *acid*, $[\alpha]_D^{20}$ +1·1° (*c*, 11·2), n_D^{36} 1·4516, and exhibiting no absorption at $\lambda > 2100$ Å (Found: C, 78·9; H, 13·3. $C_{27}H_{54}O_2$ requires C, 79·1; H, 13·2%).

Hydrogenation of the Liquid Dextrorotatory Acid.—The product, obtained as above, was an oil, $[\alpha]_D^{18}$ +1·7° (*c*, 9·4), n_D^{36} 1·4563 (Found: C, 79·2; H, 13·2%), no absorption at $\lambda > 2100$ Å.

Ozonization of the Solid Dextrorotatory Acid.—Ozonized oxygen was passed through an ice-cold solution of the acid (0·6 g.) in carbon tetrachloride (10 c.c.) for 3·5 hr., and then through saturated aqueous barium hydroxide (for determination of carbon dioxide). The solvent was then removed at room temperature by passage of a rapid stream of nitrogen; water (10 c.c.) was added, and the mixture heated slowly to 100° (bath) and kept there for 30 min. During these procedures the ozonization vessel was connected in series with (1) a trap cooled with solid carbon dioxide–acetone, (2) a solution of 2 : 4-dinitrophenylhydrazine in aqueous hydrochloric acid, (3) a trap, (4) saturated aqueous barium hydroxide, and (5) a soda-lime tube; a slow current of nitrogen was maintained. The aqueous ozonization mixture was then cooled with ice and filtered, and the filtrate (*a*) put aside. The carbon tetrachloride solution which collected in the cooled trap was washed with aqueous 5% potassium hydroxide (3 × 3 c.c.), and the alkaline extract distilled under a current of nitrogen into a solution of 2 : 4-dinitrophenylhydrazine in aqueous hydrochloric acid until onlya few c.c. remained (no precipitate of 2 : 4-dinitrophenylhydrazones was obtained). The residual alkaline solution was then acidified (sulphuric acid) and distilled. The distillate was combined with the above filtrate (*a*), and neutralized with 0·1N-sodium hydroxide (phenolphthalein) (this titration indicated a yield of about 0·7 mol. of acetic acid). The neutralized solution was concentrated to a small bulk, *p*-bromophenacyl bromide (0·27 g.) in ethanol (5 c.c.) added, and the mixture refluxed for 2 hr. The product, after crystallization from methanol, had m. p. 81—83°, undepressed on admixture of an authentic specimen of *p*-bromophenacyl acetate, m. p. 84—85° (Found: Br, 31·0. Calc. for $C_{10}H_9O_3Br$: Br, 31·1%). The amount of carbon dioxide collected during the ozonization and the decomposition of the ozonide corresponded to about 0·3 mol. During the decomposition of the ozonide a slight precipitate, identified as acetaldehyde 2 : 4-dinitrophenylhydrazone, was formed. No oxalic acid was found among the ozonization products.

Isolation of the Lævorotatory Acid.—From the hydrolysis of the extract (*A*) already described a methanol-insoluble product (i) resulted (see above). This was combined with similar material from earlier work, and the product (about 250 g.) refluxed with potassium hydroxide (65 g.) in methanol (320 c.c.) and benzene (1280 c.c.) for 215 hr. (a much shorter period is probably sufficient). On dilution with water and acidification (hydrochloric acid) troublesome emulsions were formed. These were shaken with several portions of ether and, after being kept overnight, as much as possible of the clear organic layers was removed. The remaining emulsified portion was poured on sodium sulphate, and again extracted with ether. The combined benzene–ether extracts were dried (Na_2SO_4) (attempts to wash them with water until free from hydrochloric acid had to be abandoned owing to the formation of persistent emulsions), and concentrated (to about 700 c.c.), and to the concentrate methanol (1700 c.c.) was added. Next

morning the precipitated tar was removed and the remaining solution evaporated. The residue was refluxed with 15% ethanolic potassium hydroxide (80 c.c.) for 4 hr. (to hydrolyze any esters formed in the previous stage), and the product obtained on acidification (hydrochloric acid) was collected by means of ether. The solvent was then evaporated, and water removed from the residue azeotropically by the addition of benzene, followed by evaporation to dryness under reduced pressure on the steam-bath. The product was dissolved in hot light petroleum (250 c.c.), and the solution kept overnight at about 10°. The precipitated material, removed by filtration, had after recrystallization from ethyl acetate, m. p. 72—73·5°, and corresponded in its properties to those given by Ginger and Anderson (*J. Biol. Chem.*, 1945, **157**, 213) for the alcohol "phthiocerol." The remaining light petroleum solution was evaporated, and the residue extracted with several portions of hot methanol (altogether 500 c.c.). After removal of the methanol, the residue was taken up in ether, and then shaken with 5% aqueous potassium hydroxide (200 c.c.). The ethereal layer which contained the potassium salts was separated (pouring a few c.c. of methanol along the walls of the separating-funnel facilitated the separation of the layers) and evaporated, and the residue dried (desiccator). The product was then dissolved in ether (150 c.c.) by heat under reflux in a few minutes, and kept overnight at 10°. The fine, hard precipitate (more concentrated ethereal solutions gave gelatinous products) was collected, and this process was repeated with fresh quantities of ether. The product, which was very sparingly soluble in cold ether, was then converted into the free acid by the addition of dilute hydrochloric acid (steam-bath). The acid (10·5 g.), isolated by means of ether, had $[\alpha]_D^{18}$ −8·7° (*c*, 20·9). A further quantity (2·5 g.) of the acid showing the same specific rotation (*c*, 25·2) was obtained from the *iso*propyl ether extract (*B*) of the bacterial cells essentially by the same procedure as described above for the acetone extract (*A*). These products were combined and converted into the methyl esters by refluxing methanol (150 c.c.) and concentrated sulphuric acid (3 c.c.) during 18 hr. (a shorter period is sufficient). The product, isolated in the usual manner, afforded on distillation the fractions: (1) 195—210°/0·4 mm. (0·6 g.), $[\alpha]_D^{13}$ −8·1° (*c*, 12·6); (2) 210—222°/0·3 mm. (2·2 g.), $[\alpha]_D^{13}$ −8·8° (*c*, 11·35); and (3) 223—226°/0·3 mm. (8·9 g.), $[\alpha]_D^{13}$ −10·3° (*c*, 26·2).

Fraction (3) (Found: C, 80·1; H, 13·2. Calc. for $C_{32}H_{64}O_2$: C, 80·0; H, 13·3%) exhibited no high-intensity absorption of ultra-violet light at $\lambda > 2100$ Å. A sample (2 g.) was hydrolysed by potassium hydroxide (2 g.) in anhydrous refluxing methanol (20 c.c.) for 6 hr. After the mixture had been kept overnight at 10° the resulting potassium salt was separated from the solution. The free acid, obtained by treatment with dilute hydrochloric acid and extraction with ether, was a white solid, m. p. 30° (microscope hot-stage), $[\alpha]_D^{21}$ −6·9° (*c*, 16·8), n_D^{35} 1·4541 (Found: C, 80·1; H, 13·2%; equiv., 464. Calc. for $C_{31}H_{62}O_2$: C, 79·8; H, 13·3%; equiv., 466). The m. p., specific rotation, and refractive index showed no change after the acid (0·5 g.) had been shaken in glacial acetic acid (50 c.c.) under hydrogen (2 atm.) in the presence of platinic oxide for 24 hr. The acid formed a *p*-bromophenacyl ester, m. p. 31·5° (microscope hot-stage) (Found: C, 70·7; H, 10·1. Calc. for $C_{39}H_{67}O_3Br$: C, 70·6; H, 10·1%).

Stepwise Degradation of the Lævorotatory Acid.—The above acid (3·3 g.) was heated with bromine (5·8 g.) in the presence of red phosphorus (0·25 g.) on a steam-bath for 8 hr. After removal of the excess of bromine under diminished pressure, the product was shaken with water, and the mixture set aside at the room temperature for 3 hr. The product, collected by means of ether, was then heated with a solution of potassium hydroxide (3 g.) in water (120 c.c.) at 100° for 24 hr. Acidification with dilute hydrochloric acid, followed by extraction with ether, afforded the crude hydroxy-acid. This was dissolved in dry benzene (100 c.c.) and oxidized by means of lead tetra-acetate (3·2 g.; added in two portions) at 60° (bath) for 3 hr. After decomposition of the excess of lead tetra-acetate by addition of a solution of glycerol in glacial acetic acid, the solution was filtered, washed with dilute hydrochloric acid, then with water, and dried (Na_2SO_4). The benzene was distilled off, and the residue, dissolved in ether, was shaken with 5% aqueous potassium hydroxide. The ethereal layer was separated and kept overnight at about 10°, and the precipitated potassium salts were removed. The remaining solution was evaporated, and the residue heated with formic acid (98%; 10 c.c.) and hydrogen peroxide (30%; 3 c.c.) at 60° (bath) for 2 hr. (to oxidize any aldehydes present). After dilution with water, the mixture was extracted with ether, and the ethereal extract washed with 5% aqueous potassium hydroxide, then with water, and dried (Na_2SO_4). Removal of the solvent left a *ketone* (0·8 g.), b. p. 190—200° (bath)/0·02 mm., $[\alpha]_D^{18}$ +2·1° (*c*, 7·8) (Found: C, 81·9; H, 13·8. $C_{30}H_{60}O$ requires C, 82·6; H, 13·8%). It formed a *semicarbazone*, m. p. 69—70° after crystallization from ethanol (Found: C, 75·0; H, 13·1; N, 8·8. $C_{31}H_{63}ON_3$ requires C, 75·5; H, 12·8; N, 8·5%).

One of us (J. D. C.) participated in the work during leave of absence from the Mount Sinai Hospital, New York.

We thank Professor Sir Robert Robinson, O.M., F.R.S., for his interest, Glaxo Laboratories Ltd. for the provision of the extracts of tubercle bacilli, and Dr. L. N. Short for the infra-red spectra. The work of one of us (J. D. C.) has been facilitated by grants from the Rockefeller Foundation and the Dazian Foundation, New York. This work was carried out during the tenure of an I.C.I. Fellowship (N. P.).

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, November 30th*, 1953.]

Constituents of the Lipids of Tubercle Bacilli. Part III. Mycolipenic Acid.*

By N. POLGAR.

[Reprint Order No. 4851.]

Degradative studies of mycolipenic acid, a dextrorotatory acid from the lipids of tubercle bacilli, are reported which have shown that this acid is (+)-2 : 4 : 6-trimethyltetracos-2-enoic acid † (cf. Polgar and Robinson, *Chem. and Ind.*, 1951, 685).

IN the preceding Part,* the separation of the dextrorotatory acids of the lipids of tubercle bacilli (human type) into a solid and a liquid acid was described, both of which were shown to contain an αβ-unsaturated acid. The degradative studies of the αβ-unsaturated constituent of the solid acid are now reported.

Ozonization of the solid acid yielded pyruvic acid (isolated as its 2 : 4-dinitrophenylhydrazone). This showed that the αβ-unsaturated acid has the terminal grouping $\cdot C(:CMe)\cdot CO_2H$.

Oxidation of the methyl ester derived from the solid acid, by means of potassium permanganate in acetone, indicated that another main constituent of this material is an ester of a saturated branched-chain acid. This was unaffected by the oxidation, whereas the methyl ester of the αβ-unsaturated acid, now termed mycolipenic acid, was converted into an acid (II), $C_{24}H_{48}O_2$, forming a *p*-bromophenacyl ester of m. p. 68°, and small amounts of a methyl ketone (III), $C_{21}H_{43}\cdot CO\cdot CH_3$ (positive iodoform test), characterized as its semicarbazone, m. p. 94—95°. The same ketone was obtained on a Wieland–Barbier degradation of the acid (II), thus indicating that this acid has one alkyl (methyl) substituent in the α-position to the carboxyl group. These results disclosed that mycolipenic acid has the terminal grouping $\cdot CHMe\cdot CH{:}CMe\cdot CO_2H$.

The acid (II) had $[\alpha]_D$ +7·1°. Bromination (Hell–Volhard–Zelinsky method), followed by reaction of the α-bromo-acid bromide with methanol, and dehydrobromination of the resulting bromo-ester by refluxing pyridine, gave an αβ-unsaturated ester (IV) ($\lambda_{max.}$ 2160 Å; log ε 4·14) which exhibited $[\alpha]_D$ +13·3°. The rotatory power of this ester already indicated (cf. Jocelyn and Polgar, *J.*, 1953, 132) that there is an asymmetric centre adjacent to the αβ-double bond, *i.e.*, at $C_{(4)}$. This was confirmed by oxidation of the ester, by means of potassium permanganate in acetone, which, similarly to the oxidation of the initial αβ-unsaturated ester (see above), yielded an acid (V) and a by-product ketone (VI). The acid (V) had $[\alpha]_D$ about +7° and gave an amide of m. p. 107—108° which corresponded to the m. p. (108°) recorded (Schneider and Spielman, *J. Biol. Chem.*, 1942, **142**, 345) for (±)-2-methyleicosanoamide. The ketone (VI), yielding a semicarbazone of m. p. 124—125°, was identified as *n*-eicosan-2-one by *X*-ray crystallographic studies, kindly carried out by Mrs. D. M. Crowfoot Hodgkin; an account of these studies has already been given (Bailey, Polgar, and Robinson, *J.*, 1953, 3031).

* Part II, preceding paper. An account of this work has been included in a lecture at the VIth International Congress for Microbiology, Rome, September, 1953.

† Geneva nomenclature (CO_2H = 1) is used throughout.

These results showed that mycolipenic acid is (+)-2 : 4 : 6-trimethyltetracos-2-enoic acid (I).

(I) $CH_3 \cdot [CH_2]_{17} \cdot CHMe \cdot CH_2 \cdot CHMe \cdot CH{:}CMe \cdot CO_2H$
(II) $CH_3 \cdot [CH_2]_{17} \cdot CHMe \cdot CH_2 \cdot CHMe \cdot CO_2H$
(III) $CH_3 \cdot [CH_2]_{17} \cdot CHMe \cdot CH_2 \cdot CO \cdot CH_3$
(IV) $CH_3 \cdot [CH_2]_{17} \cdot CHMe \cdot CH{:}CMe \cdot CO_2Me$
(V) $CH_3 \cdot [CH_2]_{17} \cdot CHMe \cdot CO_2H$
(VI) $CH_3 \cdot [CH_2]_{17} \cdot CO \cdot CH_3$

An early oxidation experiment involving a mixture of the dextrorotatory acids is described in the Experimental section.

Experimental

Ultra-violet absorption spectra were determined in methanol, specific rotations in ether, 0·5-dm. tubes being used.

Ozonization of the Solid Dextrorotatory Acid.—Ozonized oxygen was passed into an ice-cooled solution of the solid dextrorotatory acid (Part II, *loc. cit.*) (0·5 g.) in carbon tetrachloride (10 c.c.) for 15 min. Water (10 c.c.) was then added, and the product heated at 100° for 0·5 hr. (the carbon tetrachloride was allowed to evaporate during this procedure). After cooling, the water-insoluble products were filtered off, and a 0·1% solution of 2 : 4-dinitrophenylhydrazine in aqueous hydrochloric acid was added to the filtrate. The precipitated product was collected and triturated with aqueous 5% sodium hydrogen carbonate; the solution was then filtered and the filtrate acidified with dilute hydrochloric acid. The product had m. p. 213—214° (microscope hot-stage) (Found : N, 20·8. Calc. for $C_9H_8O_6N_4$: N, 20·9%), undepressed by an authentic specimen of pyruvic acid 2 : 4-dinitrophenylhydrazone. In an earlier experiment (cf. Part II) in which ozonized oxygen was passed through a solution containing the dextrorotatory solid acid for 3·5 hr., only acetic acid was found in the aqueous solution of the ozonization products.

Oxidation of the Methyl Ester of the Solid Dextrorotatory Acid.—To a solution of the ester (1 g.; obtained by refluxing the acid with 5% methanolic sulphuric acid) in dry acetone (100 c.c.), heated under reflux with stirring, powdered potassium permanganate was added in small portions until the rate of oxidation became very slow (about 4 hr.). The precipitated manganese dioxide was filtered off and washed with dry ether. The combined filtrates were evaporated, and the residue, after addition of water and acidification (hydrochloric acid), was extracted with ether. The product (0·6 g.) obtained on evaporation of the ethereal extract contained only little acidic material (it required 1·1 c.c. of 0·1N-sodium hydroxide for neutralization). The neutralized (phenolphthalein) solution was extracted with ether, the ethereal solution evaporated, and the product separated into a ketone and a non-ketone fraction with the aid of Girard's P reagent (1 g.). The ketone fraction (4-methyldocosan-2-one), isolated in the usual manner, distilled at 205—210° (bath)/0·01 mm., and yielded a *semicarbazone*, m. p. 94—95° (Found : C, 72·85; H, 12·3; N, 10·5. $C_{24}H_{49}ON_3$ requires C, 72·9; H, 12·4; N, 10·6%). The non-ketone fraction (about 0·5 g.) (Found : C, 78·6; H, 13·2%) exhibited no high-intensity absorption in the ultra-violet, and had $[\alpha]_D$ +0·8° (*c*, 12·6).

The above manganese dioxide precipitate was dissolved by the addition of sodium hydrogen sulphite and dilute hydrochloric acid, and the product extracted with ether. Re-extraction of the ethereal solution with 5% aqueous potassium hydroxide, followed by acidification of the aqueous extract, afforded 2 : 4-*dimethyldocosanoic acid* (II) (0·3 g.), m. p. 34—35° (crude product), $[\alpha]_D^{16}$ +7·1° (*c*, 5·9) (Found : C, 78·3; H, 13·3%; equiv., by titration with aqueous-methanolic 0·1N-sodium hydroxide, 369·9. $C_{24}H_{48}O_2$ requires C, 78·3; H, 13·1%; equiv., 368). Its *p-bromophenacyl* ester had m. p. 68° after crystallization from ethanol (Found : C, 67·8; H, 9·4; Br, 14·1. $C_{32}H_{53}O_3Br$ requires C, 68·0; H, 9·4; Br, 14·2%).

No oxalic acid was found in the aqueous mother-liquors of the above oxidation products.

Wieland–Barbier Degradation of the Preceding Acid Oxidation Product (II).—The methyl ester of this acid (0·23 g.; obtained by refluxing the acid with methanolic sulphuric acid) in benzene (10 c.c.) was added to a Grignard solution from bromobenzene (6·7 g.) and magnesium (1 g.) in ether (20 c.c.), and the mixture refluxed for 2 hr. The solvent was then distilled off on a steam-bath as far as possible, and benzene (5 c.c.) added to the residue, and then slowly distilled off. After being heated on the steam-bath for a further hour, the residue was cooled, and decomposed by means of ammonium chloride and ice. The product, collected in ether, was then distilled in steam (to remove diphenyl). The non-volatile part was extracted with ether, the ethereal solution evaporated, and the resulting crude alcohol dehydrated by refluxing formic acid (98%; 5 c.c.) for 1·5 hr. After dilution with water, the product was extracted with

ether, and the ethereal extract washed successively with water, 5% aqueous potassium hydroxide, and water, and dried (Na_2SO_4). The product obtained on evaporation of the ether was dissolved in carbon tetrachloride (5 c.c.), and a stream of ozonized oxygen passed into the solution for 10 min., while cooling with ice. The solvent was then evaporated under reduced pressure at 30° (bath), water (10 c.c.) added to the residue, and the mixture slowly heated to 100° and kept there for further 20 min. The product, collected with ether, was kept with a solution of powdered potassium permanganate in acetone (5 c.c.) at room temperature for 10 min. Sodium hydrogen sulphite and dilute hydrochloric acid were then added. The product was extracted with ether, and the ethereal solution washed successively with water, 5% aqueous potassium hydroxide, and water. Evaporation of the dried (Na_2SO_4) ethereal extract, followed by purification of the residual product with the aid of Girard's P reagent (1 g., in 10 c.c. of methanol) yielded a ketone (III) forming a semicarbazone, m. p. 92—93° (from ethanol) (Found: N, 10·8%), undepressed on admixture with the semicarbazone (m. p. 94—95°) of the ketone obtained by the oxidation of the methyl ester of the solid dextrorotatory acid (see preceding section). The parent ketone, regenerated by heating of the semicarbazone with aqueous oxalic acid, gave a positive iodoform test.

Bromination of the Acid Oxidation Product (II) *and Dehydrobromination of the α-Bromo-ester.*—To a mixture of the acid (0·27 g.) and red phosphorus (0·04 g.) at 90° (bath) was added dropwise dry bromine (slight excess) with frequent shaking. After a further 3 hours' heating some more bromine (few drops) was added, and heating continued for another 3 hr. The product was cooled, dry methanol (10 c.c.) added, and the mixture refluxed for 1 hr. Dilution with water and extraction with ether gave the crude bromo-ester. This ester (0·3 g.) and dry pyridine (7 c.c.) were refluxed for 17 hr. After addition of dilute hydrochloric acid, the product was collected with ether and distilled. The unsaturated ester (IV) distilled at 200—210° (bath)/0·02 mm., and had $[\alpha]_D^{21}$ +13·3° (*c*, 3·16), n_D^{18} 1·4590 (Light absorption: Max., 2160 Å; log ε 4·14).

Oxidation of the Unsaturated Ester (IV).—The preceding ester (about 0·1 g.) in acetone (25 c.c.) was oxidized with potassium permanganate as above. The precipitated manganese dioxide was filtered off and washed with ether. The combined filtrates were evaporated, and the residual product was refluxed with ethanolic potassium hydroxide for 1 hr. After acidification, the mixture was extracted with ether, and the ethereal extract washed with 5% potassium hydroxide solution. The non-acid material remaining in the ethereal layer distilled at 160—170° (bath)/0·07 mm. It formed a semicarbazone which had m. p. 122—123° after one crystallization from ethanol; further crystallizations from the same solvent raised the m. p. to 124—125°. Only a few mg. resulted which were reserved for *X*-ray crystallographic studies (cf. Bailey, Polgar, and Robinson, *loc. cit.*).

The precipitated manganese dioxide was treated with sodium hydrogen sulphite and dilute hydrochloric acid, and the mixture extracted with ether. Re-extraction of the ethereal solution with 5% aqueous potassium hydroxide, followed by acidification of the aqueous extract, yielded 2-methyleicosanoic acid (V), $[\alpha]_D$ about +7° (*c*, 1·6). It was characterized as the amide, m. p. 107—108° after crystallization from methanol (Found: C, 77·7; H, 12·8. Calc. for $C_{21}H_{43}ON$: C, 77·5; H, 13·2%).

Oxidation of a Mixture of the Dextrorotatory Acids.—In early experiments preceding the work described in Part II (*loc. cit.*) a mixture of the dextrorotatory acids (0·5 g.), isolated by distillation of the methyl esters essentially as described in Part I (Polgar, *Biochem. J.*, 1948, **42**, 206) and having $[\alpha]_D^{16}$ +8·3° (*c*, 11·8) (Found: C, 78·2; H, 12·4%), was subjected to an oxidation with potassium permanganate in acetone in the manner already described. After evaporation of the solvent, the precipitated manganese dioxide was removed by the addition of aqueous sodium hydrogen sulphite and dilute sulphuric acid, and the product extracted with ether. Re-extraction of the ethereal solution with 5% aqueous potassium hydroxide, and then with water, followed by acidification of the aqueous phase, afforded a mixture of acids which yielded a *p*-bromophenacyl ester, m. p. 65—66° after crystallization from ethanol (Found: C, 68·2; H, 9·2; Br, 13·9%). The non-acid material which remained in the ethereal layer gave, with the aid of Girard's P reagent, a ketone, forming a semicarbazone, m. p. 89—90° (Found: C, 73·0; H, 12·1; N, 10·8%). An acid yielding the same *p*-bromophenacyl ester as above (Found: C, 67·85; H, 9·6; Br, 14·15%) was obtained on ozonization (2 hr.) of the above mixture of the dextrorotatory acids (0·3 g.) in carbon tetrachloride (7 c.c.), followed by the action of hydrogen peroxide (30% w/v) and formic acid (98%) on the ozonization product.

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, November 30th*, 1953.]

Constituents of the Lipids of Tubercle Bacilli. Part IV. Mycoceranic Acid.*

By N. Polgar.

[Reprint Order No. 4852.]

Degradative studies of a lævorotatory acid isolated from the lipids of tubercle bacilli are reported. It is found that the acid, now termed mycoceranic acid, has the structure $CH_3{\cdot}[CH_2]_n{\cdot}CHMe{\cdot}CH_2{\cdot}CHMe{\cdot}CH_2{\cdot}CHMe{\cdot}CO_2H$ where n is probably 21 (cf. *Chem. and Ind.*, 1953, 353).

The isolation of a lævorotatory acid from the lipids of tubercle bacilli (human type) was described in Part II.* The present communication concerns degradative studies of this acid.

The acid was already shown to be saturated; titration gave a result in close agreement with $C_{31}H_{62}O_2$. A stepwise degradation described in Part II (*loc. cit.*), involving oxidation of the derived α-hydroxy-acid by means of lead tetra-acetate, gave a ketone; the same ketone was also obtained by a Wieland–Barbier degradation. This indicated that the parent acid has one alkyl substituent in the α-position to the carboxyl group.

Bromination of the lævorotatory acid (Hell–Volhard–Zelinsky method) and dehydrobromination of the α-bromo-derivative with pyridine gave an αβ-unsaturated acid ($\lambda_{max.}$ 2180 Å; log ε 4·06) which on ozonization yielded pyruvic acid.

These experiments indicated that the parent saturated acid has the terminal group $\cdot CHMe{\cdot}CO_2H$.

The methyl ester of the αβ-unsaturated acid exhibited $[\alpha]_D$ −10·2°, which indicated the presence of an asymmetric centre adjacent to the αβ-double bond (Part III, *loc. cit.*; cf. also Jocelyn and Polgar, *J.*, 1953, 132), and this was confirmed by oxidation of the ester, by potassium permanganate in acetone, to an acid having $[\alpha]_D$ −5·8°, and a by-product ketone. Both oxidation products were closely analogous to those resulting on oxidation of mycolipenic acid, already shown to be 2 : 4 : 6-trimethyltetracos-2-enoic acid (Part III), the acid forming a *p*-bromophenacyl ester of m. p. 68°, and the ketone yielding a semicarbazone, m. p. 92·5° (as compared with the previous m. p.s 68°, and 94—95°, respectively). This suggested that the above αβ-unsaturated acid must have the structure (II) analogous to that of mycolipenic acid, and differing from the latter only in the sign of the rotation, and by the length of the normal chain. It then follows that the acid and the ketone, obtained on oxidation, have the structures (III) and (IV), respectively, analogous to those of the oxidation products of mycolipenic acid.

In further experiments, the acid (III) has been subjected to the same sequence of degradative reactions which, in case of mycolipenic acid, resulted in the isolation of eicosan-2-one. Bromination of the acid, followed by reaction of the α-bromo-acid bromide with methanol, and dehydrobromination by means of pyridine, gave an αβ-unsaturated ester, with $[\alpha]_D$ −9·1°, the magnitude of the rotation again indicating the presence of an asymmetric centre adjacent to the αβ-double bond. This was oxidized, by means of potassium permanganate in acetone, to an acid (with negative rotation) and a by-product ketone. The semicarbazone of the latter had m. p. 126° (compared with 124—125° for the semicarbazone of *n*-eicosan-2-one), which indicated that the ketone has an unbranched chain.

(I) $CH_3{\cdot}[CH_2]_n{\cdot}CHMe{\cdot}CH_2{\cdot}CHMe{\cdot}CH_2{\cdot}CHMe{\cdot}CO_2H$
(II) $CH_3{\cdot}[CH_2]_n{\cdot}CHMe{\cdot}CH_2{\cdot}CHMe{\cdot}CH{:}CMe{\cdot}CO_2H$
(III) $CH_3{\cdot}[CH_2]_n{\cdot}CHMe{\cdot}CH_2{\cdot}CHMe{\cdot}CO_2H$
(IV) $CH_3{\cdot}[CH_2]_n{\cdot}CHMe{\cdot}CH_2{\cdot}CO{\cdot}CH_3$

These results showed that the lævorotatory acid, now termed mycoceranic acid, has the structure (I), where n is probably 21. The length of the normal chain requires confirmation by an *X*-ray crystallographic study of the preceding ketone.

* Parts II and III, preceding papers. An account of this work was included in a lecture at the VIth International Congress for Microbiology, Rome, September, 1953.

A point of interest is that mycoceranic acid (I), as well as the αβ-unsaturated acid (II), and the acidic degradation products having an asymmetric centre in the α-position to the carboxyl group, exhibit lævorotation. Mycolipenic acid itself, and also its degradation products with an asymmetric centre in the α-position to the carboxyl grouping (structurally differing from those of mycoceranic acid only by the length of the normal chain) are dextrorotatory. Thus mycoceranic and mycolipenic acid possess opposite configurations.

Experimental

Ultra-violet absorption spectra were determined in methanol by Dr. F. B. Strauss, with the assistance of Mr. F. Hastings. Specific rotations were measured in ether, 0·5-dm. tubes being used.

Wieland–Barbier Degradation.—The methyl ester of the lævorotatory acid (described in Part II, *loc. cit.*) (2·2 g.) in benzene (15 c.c.) was added dropwise to a Grignard solution from bromobenzene (20 g.) and magnesium (3· g.) in ether (45 c.c.), and the mixture refluxed for 3 hr. The solution was worked up, and the resultant alcohol dehydrated as described in Part III. The product, $[\alpha]_D^{14}$ −27·6° (*c*, 8·55), was then ozonized in carbon tetrachloride (20 c.c.) for 2 hr. On working up as previously described a ketone (0·9 g.) resulted which gave a semicarbazone, m. p. 68—69° (Found: C, 75·4; H, 12·5; N, 8·8. Calc. for $C_{31}H_{63}ON_3$: C, 75·5; H, 12·8; N, 8·5%), undepressed an admixture with the semicarbazone (m. p. 69—70°) of the ketone obtained by the stepwise degradation described in Part II (*loc. cit.*).

Bromination of the Lævorotatory Acid and Dehydrobromination of the α-Bromo-ester.—The lævorotatory acid (0·4 g.) was heated with bromine (slight excess) in the presence of red phosphorus (0·03 g.) for 6 hr. as previously described, and the resulting crude acid bromide converted into the methyl ester by means of methanol (10 c.c.). This bromo-ester, in refluxing anhydrous pyridine (6 c.c.; 24 hr.), afforded an αβ-unsaturated *ester*, b. p. 215—220° (bath)/0·05 mm. (0·31 g.), $[\alpha]_D^{13}$ −10·2° (*c*, 6·25) (Found: C, 80·5; H, 12·9. $C_{32}H_{62}O_2$ requires C, 80·3; H, 13·0%). Light absorption: Max., 2180 Å; log ε 4·06. The acid, obtained by hydrolysis with ethanolic potassium hydroxide, gave on ozonization according to the procedure described in Part III (*loc. cit.*) pyruvic acid, isolated as its 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 214—215° (microscope hot-stage).

Oxidation of the αβ-Unsaturated Ester.—The above ester (0·3 g.) in acetone (25 c.c.) was oxidized with potassium permanganate and the product worked up as described in Part III. The main product was an acid (III), $[\alpha]_D^{13}$ −5·8° (*c*, 12·09), which formed a p-*bromophenacyl* ester, m. p. 68° after crystallization from ethanol (Found: C, 70·2; H, 9·7. $C_{36}H_{61}O_3Br$ requires C, 69·6; H, 9·8%). As a by-product, small amounts of a ketone (IV) were isolated which was characterized as its *semicarbazone*, m. p. 92·5° (sintering at 91°) after one crystallization from ethanol (the m. p. may rise somewhat on further crystallizations) (Found: C, 74·0; H, 12·3. $C_{28}H_{57}ON_3$ requires C, 74·5; H, 12·6%).

Degradation of the Acid (III).—This was carried out by the procedure given in Part III for the degradation of the acid oxidation product of mycolipenic acid. Bromination and dehydrobromination, followed by treatment of the α-bromo-acid bromide with methanol, gave an αβ-unsaturated ester, $[\alpha]_D^{17}$ −9·1° (*c*, 10·81), which was oxidized with potassium permanganate in acetone. The oxidation products were an acid yielding a p-*bromophenacyl* ester, m. p. 82—83° (from ethanol) (Found: C, 68·7; H, 9·4; Br, 13·9. $C_{33}H_{55}O_3Br$ requires C, 68·4; H, 9·5; Br, 13·8%), and a ketone, which formed a semicarbazone of m. p. 126° after crystallization from ethanol.

Dyson Perrins Laboratory, Oxford University. [*Received, November 30th,* 1953.]

A Dilatometric Study of the Transition in Methyl Alcohol.

By L. A. K. Staveley and M. A. P. Hogg.

[Reprint Order No. 4563.]

Advantage has been taken of the small solubility of methyl alcohol in *iso*pentane at low temperatures to investigate the volume changes which occur on the solidification of the alcohol and also at what has hitherto been considered as the single λ-point transition which this substance appeared to possess. It has been found, however, that there are two transitions, separated by only 3°. The upper transition is no doubt what has previously been regarded as the single transition, but it seems that this sets in much more abruptly than has been supposed, and it is probably more of the nature of a first-order phase change than a λ-point. It is the lower transition which is probably gradual in character, and its discovery is briefly discussed in the light of other information about solid methyl alcohol, and in particular in relation to recent crystallographic work.

The contraction in volume on solidification is 2·75 c.c./mole. On cooling, there is a further contraction of 0·49 c.c./mole at the upper transition at 159° K, and another contraction of ~0·14 c.c./mole at the lower transition.

The transition in methyl alcohol has been the subject of several recent papers. This transition occurs at ~159° K, *i.e.*, about 16° below the m. p. Cooke and Drain (*Proc. Phys. Soc.*, 1952, **65**, 894) examined the change in the proton magnetic resonance line width which accompanies it. Tauer and Lipscomb (*Acta Cryst.*, 1952, **5**, 606) carried out careful *X*-ray diffraction studies of the high- and the low-temperature form, and proposed structures for them. These authors consider that the transformation from the high- to the low-temperature form involves only a puckering of the infinite chains of hydrogen bonds to give more compact packing, these displacements being confined to planes normal to the direction of the chains. While this work rules out any possibility that the transition is in any way connected with the loss or gain of intermolecular rotation (or of intramolecular rotation of hydroxyl groups), Tauer and Lipscomb have nevertheless been able to account for the dielectric-constant changes associated with this transition (Smyth and McNeight, *J. Amer. Chem. Soc.*, 1936, **58**, 1597), and have also pointed out that their proposed structure for the low-temperature form is consistent with Weltner and Pitzer's conclusion (*ibid.*, 1951, **73**, 2606) that solid methanol probably has no residual entropy at the absolute zero.

A different structure for the high-temperature form, based on *X*-ray powder photographs, has been proposed by Dreyfus-Alain and Viallard (*Compt. rend.*, 1952, **235**, 536).

In reporting the results of a comparison of the thermodynamic properties of methyl alcohol and methyl deuteroxide, which included information about the transitions in the two solids, Staveley and Gupta (*Trans. Faraday Soc.*, 1949, **45**, 50) commented on the tendency of solid methyl alcohol, after being rapidly frozen in liquid air and then warmed in a glass container, to shatter the vessel. They suggested that this might be because the transformation of the high-temperature into the low-temperature form may be accompanied by a volume increase, since on very rapid cooling in liquid air the high-temperature form tends to be preserved in a metastable state, but changes spontaneously to the more stable form on warming. The experiments to be described were carried out with the object of testing this suggestion about the direction of the volume change. The guess proved to be wrong. The high-temperature form passes into the low-temperature form with a volume decrease. The interesting discovery was made, however, that solid methyl alcohol has *two* transitions, only about 3° apart. The lower of these is associated with only a very small volume change. The higher is no doubt what has hitherto been regarded as the single transition, and our work shows that this sets in much more abruptly than had been supposed, so that it may be a first-order phase change rather than a λ-point.

Experimental

The choice of a suitable dilatometric fluid presented some difficulty. The requirements were that it should remain liquid down to at least 140° K (without becoming too viscous), and that the mutual miscibility with methyl alcohol should be as low as possible. After preliminary experiments, it was decided to use *iso*pentane. The m. p. of methyl alcohol in the presence of *iso*pentane was found to be about 1° less than that of the pure alcohol. This means that a saturated solution of *iso*pentane in methyl alcohol contains about 1·3 moles % of the hydrocarbon at 175° K. The solubility of the alcohol in the *iso*pentane seemed to be not more than one-fifth of this. Since the mutual miscibility of the liquids at the m. p. of the alcohol is so small, and in view of the dissimilarity in the shapes of the two molecules, it seems very unlikely that *solid* methyl alcohol dissolves appreciable quantities of *iso*pentane.

The dilatometer used was that described by Mandleberg and Staveley (*J.*, 1950, 2736). In the first experiment, however, the bulb of the dilatometer shattered when being warmed with solid methyl alcohol in it, so for all later experiments the dilatometer was slightly modified by enclosing within it a loose inner tube into which the capillary of the dilatometer projected, as shown in Fig. 1. Even after the inner tube was shattered it was still possible to continue

Fig. 1.

Fig. 2.

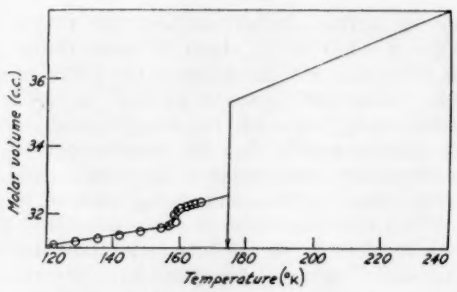


Fig. 1. *Dilatometer bulb, modified for experiments on methyl alcohol.* 1, *Loose inner tube*; 2, *re-entrant tube for thermocouple*; 3, *calibrated capillary tubing.*

Fig. 2. *Plot of the molar volume of solid and liquid methyl alcohol against temperature. The melting-point is indicated by the arrow.*

making measurements on the solid alcohol, but it was obviously undesirable to allow the alcohol to melt and to re-freeze it once the inner tube was broken. Accordingly, after the dilatometer had been filled, the alcohol was frozen and all experiments on the solid were carried out before any of the alcohol was allowed to melt; then, finally, the alcohol was melted to determine the volume change on melting. Two separate series of experiments were carried out in this way.

To fill the dilatometer, it was cooled in a bath of solid carbon dioxide and acetone, and a known weight of methyl alcohol (~15 g.) was sucked into the inner tube, sufficient almost to fill it. In order to de-gas the alcohol it was placed in a bath of melting carbon disulphide (m. p. —110° C), so that the alcohol froze but remained above the transition temperature. It was then pumped out, melted, and the process repeated. Finally, with the methyl alcohol solid, the remaining space in the dilatometer was filled by admitting de-gassed *iso*pentane.

The conversion of the high-temperature form (*i.e.*, that stable above 159° K) into the low-temperature form was attended by considerable supercooling. Even after being kept for 18 hr. below 159° K, a spontaneous evolution of heat about 30° below this temperature when the dilatometer was being warmed showed that some of the high-temperature form was still present. The procedure finally adopted was to cool the dilatometer to about 120° K, and then warm it

very slowly to about 157° K, where it was kept for 1 hr. before being cooled again. After this, successive runs gave reproducible results.

The methyl alcohol used was a middle cut from a fractionation; it was freshly dried over lime and redistilled before use.

Results.—An overall picture of the volume relationships in methyl alcohol over a temperature range covering both the transitions and melting is given by Fig. 2, in which the molar volume is plotted against temperature. It will be seen that conversion of the low-temperature form into the high-temperature form at ~159° K is accompanied by a volume increase. This amounts to 0·49 c.c./mole, which is about 18% of the volume increase of 2·75 c.c./mole associated with melting. The only other value for the latter quantity is due to Korber (*Ann. Physik*, 1912, **37**, 1024), *viz.*, 2·4 c.c./mole.

In Fig. 2, the small transition which we have found to precede the main one is not apparent, but it is just discernible as a kink in the curve in Fig. 3, which is a plot, on a larger scale, of the

FIG. 3.

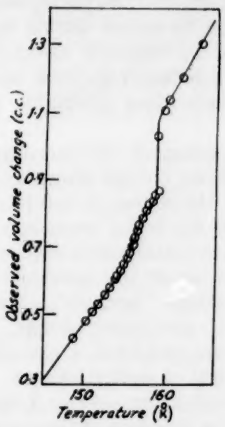


FIG. 4.

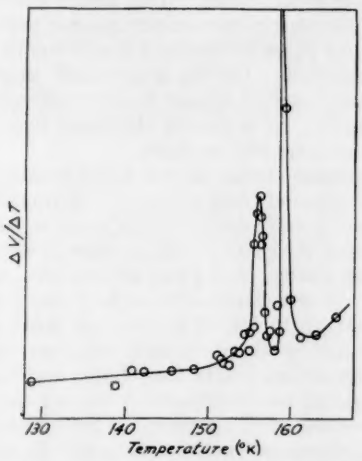


FIG. 3. *Showing the apparent change in volume of the contents of the dilatometer with temperature in the region of the two transitions.*

FIG. 4. *Plot of $\Delta V/\Delta T$ against temperature, where ΔV is the apparent increase in volume of the contents of the dilatometer for a temperature increase of ΔT. The highest observed value of $\Delta V/\Delta T$ for the upper transition was about six times the maximum value for the lower transition.*

observed volume increase of the contents of the dilatometer against temperature in the region of the transitions. To prove its existence beyond doubt, numerous measurements were made of the quantity $\Delta V/\Delta T$, where ΔV was the observed volume increase of the contents of the dilatometer when it was heated $\Delta T°$. For some of these measurements ΔT was as small as 0·5°. In Fig. 4, which is a plot of $\Delta V/\Delta T$ against T, the two transitions appear very clearly.

DISCUSSION

From our value for the volume change on melting, we estimate that at −110° C the molar volume and density are respectively 32·25 c.c./mole and 0·993 g./c.c. From the unit-cell dimensions measured at this temperature, Tauer and Lipscomb (*loc. cit.*) gave 0·972 g./c.c. for the density. They interpret the diffraction pattern of the crystals at −160° C as indicating a monoclinic structure. Their unit-cell dimensions correspond to a density of 1·020 g./c.c. at this temperature. Our dilatometric work gives a value of 1·035 g./c.c.

Undoubtedly the main transition, corresponding to the single transition previously observed in calorimetric and other studies, is that which falls at the higher temperature,

although there is not complete agreement between the value of the temperature at which the coefficient of expansion is a maximum (159° K), and that at which c_p is a maximum (157·8°, Staveley and Gupta, *loc. cit.*; 157·4°, Kelley, *J. Amer. Chem. Soc.*, 1929, **51**, 180). It would, seem, however, that the gradual rise in c_p which is noticeable several degrees before the maximum in c_p is reached must now be regarded as associated with the lower transition. Between the two transitions the coefficient of expansion falls to a low value which would seem to be almost normal. The major transition therefore sets in much more abruptly than had been supposed, and since it is clear from the crystallographic work that it involves a definite change in crystal structure, it should perhaps be regarded as a first-order phase change. The discovery of a second transition also throws light on some earlier observations made by Staveley and Gupta (*loc. cit.*) in their calorimetric investigation, namely, that equilibrium was reached only slowly in the neighbourhood of the maximum in c_p, and that here superheating was possible, while, in what were regarded as the early stages of the same transition, thermal equilibrium was rapidly attained without any appreciable superheating. This would have been difficult to understand if the transition had been like that in ammonium chloride, say, which is partly gradual and partly isothermal, where as far as we are aware it is not known for superheating to appear during the course of the transition. On the other hand, superheating is not infrequently associated with phase changes which appear to set in abruptly, such as that between rhombic and monoclinic sulphur. It is clearly the lower transition, which takes place gradually, in which equilibrium is rapidly attained.

The volume change at this lower transition cannot be estimated very accurately, but it is approximately 0·14 c.c./mole. A transition with a volume change about as small as this is that in solid deuterium sulphide at 108° K, for which the change is ~0·18 c.c./mole (Clusius and Weigand, *Z. Elektrochem.*, 1938, **44**, 674). But the latter transition involves an entropy change of ~4 cal./mole/degree, whereas the lower transition in methyl alcohol can only be associated with a very small entropy change, since the calorimetric work shows that up to 156° K c_p does not much exceed extrapolated "normal" values. The lower transition therefore only involves some very slight structural change. In this connection we may note that Tauer and Lipscomb (*loc. cit.*) proposed a monclinic unit cell containing two molecules for the low-temperature (α-form) of methyl alcohol, but that they remarked on the presence of some rather faint superlattice lines on the *X*-ray photographs, and suggested that these might be accounted for by a doubling of the unit cell due to a slight alternation in the position of the methyl groups (see Fig. 7 of their paper). It would be interesting to know whether these superlattice lines vanish at 156° K (the temperature at which the coefficient of expansion reaches a maximum for the first transition), *i.e.*, before the main transition at 159° K, and whether, therefore, the first transition is associated with the vanishing of the alternation in the position of the methyl groups just referred to, this being followed 3° later by the change into the orthorhombic modification. Finally, we may note that Cooke and Drain (*loc. cit.*) found that the proton magnetic resonance line width transition took the form "not of a steady decrease of the line width as the temperature was raised, but of a gradual replacement of the wide line by a narrow one." Since the narrow line first became detectable in their experiments at 145° K, it would seem that its appearance must be associated with the gradual onset of the lower transition, and it is interesting that the temperature recorded by Cooke and Drain as that at which the wide line was no longer detectable is 156° K, *i.e.*, that at which we find the coefficient of expansion for the *lower* transition to reach its maximum value.

INORGANIC CHEMISTRY LABORATORY, OXFORD. [*Received, August 6th*, 1953.]

Synthetic Antimalarials. Part XLIX. The Structure and Synthesis of the Dihydrotriazine Metabolite of Proguanil.*

By H. C. Carrington, A. F. Crowther, and G. J. Stacey.

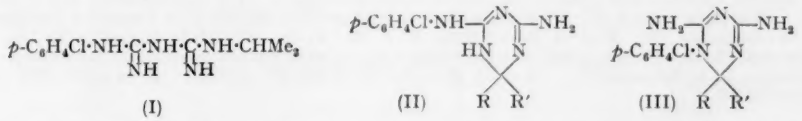
[Reprint Order No. 4755.]

The reaction between *p*-chlorophenyldiguanide and acetone under acid conditions yields a compound identical with the highly active metabolite (Crowther and Levi, *Brit. J. Pharmacol.*, 1953, **8**, 93) of the antimalarial drug "Paludrine" (proguanil, N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide). The compound is readily converted under alkaline conditions into an inactive isomer, 4-amino-6-*p*-chloroanilino-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine (II; R = R′ = Me) (cf. Birtwell, Curd, Hendry, and Rose, *J.*, 1948, 1645), the structure of which has been confirmed by the optical resolution of its 2-ethyl-2-methyl homologue (II; R = Me, R′ = Et).

From a study of the reactions of the active metabolite of proguanil, and of the condensation under both acid and basic conditions of a number of N^1-aryldiguanides bearing other substituents on one or more of the nitrogen atoms, it is concluded that the active metabolite is 4 : 6-diamino-1-*p*-chlorophenyl-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine (III; R = R′ = Me).

The isolation of a metabolite of "Paludrine" (proguanil, N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide) (I) with high antimalarial activity, from the urine of rabbits and of human volunteers receiving the drug, was described by Carrington, Crowther, Davey, Levi, and Rose (*Nature*, 1951, **168**, 1080), and a detailed account of this work has since been given by Crowther and Levi (*Brit. J. Pharmacol.*, 1953, **8**, 93). The present communication describes studies on the structure of this and related substances.

The active metabolite, strongly basic in nature, was characterised first as the picrate, and then as the free base, and was found to have the empirical formula $C_{11}H_{14}N_5Cl$, the molecule having two atoms of hydrogen less than that of proguanil itself. On treatment with warm dilute aqueous sodium hydroxide, it was readily converted into an isomeric compound which had no antimalarial activity and was identical with 4-amino-6-*p*-chloroanilino-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine (II; R = R′ = Me) which Birtwell, Curd, Hendry, and Rose (*J.*, 1948, 1645) had already prepared both by heating *p*-chlorophenyldiguanide with



(I) (II) (III)

acetone in the presence of piperidine, and by the reaction of 4-amino-1 : 2-dihydro-2 : 2-dimethyl-6-methylthio-1 : 3 : 5-triazine with *p*-chloroaniline hydrochloride. The two isomers were differentiated by the melting points of the free bases and of the picrates. The bases differed markedly in solubility, the active metabolite being the more soluble in water and the less soluble in ether. Most convenient for identification were the characteristic differences between their ultra-violet absorption spectra, both in acid (see Fig. 1) and in alkaline solution. It was later found that additional alkali was unnecessary for the isomerisation of the active metabolite. Transformation to the inactive isomer occurred when an aqueous solution of the free base was warmed, or when the solid base was heated to its melting point. Neither isomer formed a complex with copper salts.

The difficulties involved in the isolation of the metabolite limited the structural studies that could be carried out with the natural product. However, since the active metabolite was stable in neutral solution, modification of the reaction conditions used by Birtwell *et al.* (*loc. cit.*) for preparation of the inactive isomer from *p*-chlorophenyldiguanide and acetone led to formation of the active compound : the latter was obtained in very small yield by

* Part XLVIII, *J.*, 1951, 1780.

heating *p*-chlorophenyldiguanide hydrochloride with acetone in aqueous solution, and in nearly theoretical yield in the presence of a small excess of acid. The identity of the synthetic with the natural material was confirmed by melting points of the base and of the picrate, by ultra-violet absorption spectra, by its similar antimalarial activity, and by conversion into the inactive isomer.

The synthetic method* could be modified in various ways. Thus, the diguanide hydrochloride was prepared from *p*-chloroaniline hydrochloride and dicyandiamide, and without isolation brought into reaction with acetone and hydrochloric acid to give the metabolite. Alternatively, the amine, dicyandiamide, acetone, and two equivalents of hydrochloric acid could be used. Acetone could be replaced by its bisulphite compound, diethyl acetal, or *iso*propenyl acetate. In all these condensations under acid conditions the inactive isomer was not formed, even in traces. In the absence of a catalyst, acetone failed to react with *p*-chlorophenyldiguanide base. The condensation in the pre-

FIG. 1. FIG. 2.

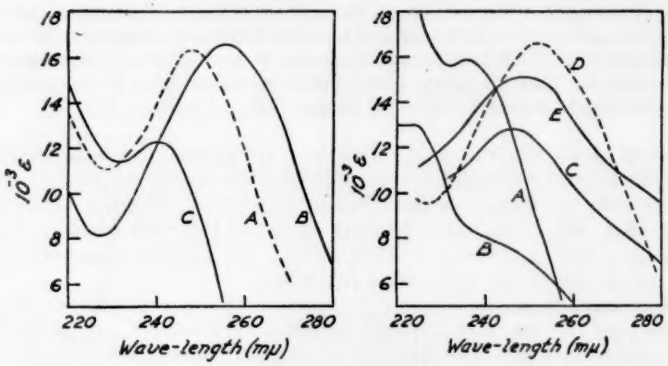


FIG. 1. *Absorption spectra in* 0·01N-HCl.

A, 4-*Amino*-6-(p-*chloro*-N-*methylanilino*)-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine* (V; X = Cl, R = Me, R′ = H, R″ = NH_2).
B, 4-*Amino*-6-p-*chloroanilino*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine* (II; R = R′ = Me).
C, 4 : 6-*Diamino*-1-p-*chlorophenyl*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine* (III; R = R′ = Me).

FIG. 2. *Absorption spectra of*: (a) 4-*Amino*-1-p-*chlorophenyl*-1 : 2-*dihydro*-2 : 2-*dimethyl*-6-*methylamino*-1 : 3 : 5-*triazine* (IX; X = Cl, R = NHMe, R′ = H): *A*, *In* 0·01N-HCl; *B*, *in* 0·1N-NaOH; *C*, *in* 0·1N-NaOH, *after* 20 *min. at* 100° *in* 0·1N-NaOH. (b) 4-*Amino*-6-p-*chloroanilino*-1 : 2-*dihydro*-1 : 2 : 2-*trimethyl*-1 : 3 : 5-*triazine* (V; X = Cl, R = H, R′ = Me, R″ = NH_2): *D*, *in* 0·01N-HCl; *E*, *in* 0·1N-NaOH.

sence of acid was a reversible reaction, for when heated with dilute aqueous acid the active compound was readily hydrolysed to acetone and the diguanide. Furthermore, the yield obtained in the condensation was dependent upon the excess of acetone used.

Somewhat later, it became known to us (personal communication from Dr. S. Farber) that workers at the Children's Hospital in Boston had independently discovered the synthetic reaction between aryldiguanides and acetone under acidic conditions, and had studied some biological properties of the products. A preliminary account of their work has been published (Modest, Farber, Foley, Pechet, and Diamond, *J. Amer. Chem. Soc.*, 1952, **74**, 855).

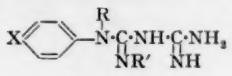
The synthesis of the active compound unfortunately made little direct contribution to a proof of its structure. It did, however, provide ample supplies of material for further study, and made possible the synthesis of analogous substances which were of great value in later structural work.

The conditions used by Birtwell *et al.* (*loc. cit.*) for the isolation of 4-amino-6-*p*-chloroanilino-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine from the reaction of *p*-chloroaniline

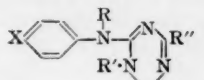
* Patent protection pending.

hydrochloride with 4-amino-1 : 2-dihydro-2 : 2-dimethyl-6-methylthio-1 : 3 : 5-triazine were such that the active metabolite, had it been the initial product, would have undergone isomerisation. The possibility existed, therefore, that the structure assigned to the inactive isomer was really that of the active substance. It was therefore decided first to seek further confirmatory evidence for the proposed structure of the inactive compound.

Valuable information was obtained from a study of the products of the condensation of N^1-aryl-N^1-methyldiguanides with acetone. For these products, structures of the type (III) are clearly impossible. N^1-*p*-Chlorophenyl-N^1-methyldiguanide (IV; X = Cl, R = Me, R′ = H) condensed with acetone in the presence of either piperidine or hydrochloric acid, giving the same product. It was considered to be 4-amino-6-(*p*-chloro-*N*-methylanilino)-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine (V; X = Cl, R = Me, R′ = H, R″ = NH_2). The ultra-violet absorption spectrum of this compound was closely similar to that of the inactive isomer, and different from that of the active metabolite (see Fig. 1). Similar results were obtained from a parallel series of experiments with N^1-methyl-N^1-phenyldiguanide (IV; X = R′ = H, R = Me). A structure such as (III) is therefore excluded for the inactive isomer.

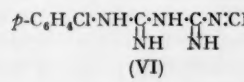


(IV)

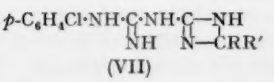


(V) Me Me

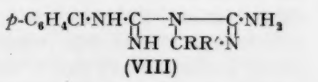
A study of analogues of the inactive isomer bearing two different substituents in the 2-position provided further evidence. *p*-Chlorophenyldiguanide condensed with ethyl methyl ketone in the presence of aqueous hydrochloric acid to give the analogue of the active body, which isomerised when heated as the base in aqueous solution. The 4-amino-6-*p*-chloroanilino-2-ethyl-1 : 2-dihydro-2-methyl-1 : 3 : 5-triazine (II; R = Me, R′ = Et) thus obtained was resolved by use of (+)-tartaric acid, the dextrorotatory base being isolated. This gave strong support to a 6-membered ring structure for the inactive isomer and its analogues. The Schiff's base form (VI) would not be resolvable, nor, in view of the tautomeric properties of the guanidine system, would the 4-membered ring structure (VII). A compound with the improbable structure (VIII) would be expected to form a copper complex. Since, of the two possible 6-membered ring structures, (III) has already been excluded, the formulation (II), suggested by Birtwell *et al.* (*loc. cit.*), seems to be well founded.



(VI)



(VII)



(VIII)

Several other derivatives of 4-amino-6-*p*-chloroanilino-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine (II; R = R′ = Me) have been prepared. With acetic anhydride it formed a diacetyl derivative, and it reacted with *p*-chlorophenyl *iso*thiocyanate to give what is believed to be 6-*p*-chloroanilino-4-*p*-chlorophenylthioureido-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine. With nitrous acid it gave 6-*p*-chloroanilino-1 : 2-dihydro-4-hydroxy-2 : 2-dimethyl-1 : 3 : 5-triazine (V; X = Cl, R = R′ = H, R″ = OH), also obtained by heating *p*-chlorophenylguanylurea with acetone and piperidine. It is noteworthy that the group attacked by nitrous acid corresponds with N^4 of the diguanide from which (II) is derived, whereas the diguanides themselves are attacked at N^2 (Curd, Davey, and Richardson, *J.*, 1949, 1732). The isomeric *N*-*p*-chlorophenyl-*N*′-guanylurea with acetone and piperidine gave what appeared to be 4-amino-1-*p*-chlorophenyl-1 : 2-dihydro-6-hydroxy-2 : 2-dimethyl-1 : 3 : 5-triazine (IX; X = Cl, R = OH, R′ = H).

Attention was next directed to a study of the active metabolite. The most likely structure for this substance, provided that no major rearrangement had occurred during the removal in the animal of two hydrogen atoms from the proguanil molecule, appeared to be 4 : 6-diamino-1-*p*-chlorophenyl-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine (III; R =

R′ = Me). In view of the ready reversibility of the synthetic reaction between *p*-chlorophenyldiguanide and acetone, it was thought unlikely that a hydrogen atom of the benzene ring was involved in the metabolic dehydrogenation. It was also considered probable that in the molecule of the active compound the three-carbon unit of acetone (the *iso*propyl group of proguanil) was linked to N^5 of the diguanide. With these restrictions, the number of possible formulæ, theoretically very large, was greatly reduced, and the next most likely structures were considered to be (VI; R = R′ = Me)—(VIII; R = R′ = Me).

The failure of the active compound to form a complex with ammoniacal copper sulphate was considered, as in the case of the inactive isomer (Birtwell *et al.*, *loc cit.*), to be evidence in favour of a cyclic structure.

In this series also, analogues with two different substituents in the 2-position should be capable of optical resolution, but efforts to carry out such resolutions have been unsuccessful. The compound (III; R = Me, R′ = Et) combined with (+)-tartaric acid to give a crystalline salt which, although prepared from equimolecular proportions of acid and base in ethanol, contained only one molecule of tartaric acid to two molecules of base. The salt appeared to be homogeneous, for it was unchanged on repeated crystallisation. Its rotation corresponded to that of the (+)-tartrate of an optically inactive base, and the base recovered from it was, in fact, inactive. Attempts to resolve (III; R = H, R′ = Pr^i) with (+)-tartaric acid, and (III; R = H, R′ = Et) with (+)-camphorsulphonic acid also failed.

Under mild conditions the active metabolite did not react with nitrous acid. Under more vigorous conditions far-reaching decomposition occurred, and no characteristic product was obtained. With *p*-chlorophenyl *iso*thiocyanate it gave only a monothiourea derivative.

It was shown by Crowther, Curd, and Rose (*J.*, 1951, 1780) that phenyldiguanide can be directly halogenated in the *p*-position of the aromatic nucleus. Halogenation experiments on the isomers formed from phenyldiguanide and acetone have shown an interesting difference in behaviour. Whereas the isomer of the inactive type resembles the diguanide in that it is readily chlorinated or brominated in the *p*-position, the compound of the active series is much more resistant.

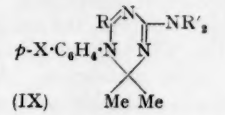
As it seemed unlikely that a rigid proof of the structure of this very labile substance would be obtained merely by degradative experiments, the condensation with acetone, under both acidic and basic conditions, of aryldiguanides bearing additional substituents in the diguanide grouping at N^2, N^4, and N^5 was studied. These substituents would be expected to limit the ways in which condensation with acetone could occur, but it should be borne in mind that, in general, the acid-catalysed condensations take place more smoothly, and in better yield, than those catalysed by bases. When condensation to an active type in acid conditions is impossible, an inactive type may be formed, as already noted in the case of the N^1-aryl-N^1-methyldiguanides. The condensation products were readily classified on the basis of their ultra-violet absorption spectra.

N^1-*p*-Chlorophenyl-N^5N^5-dimethyldiguanide (X; R = H, R′ = R″ = Me) reacted in the normal way, yielding one isomer under acidic, and the other under basic, conditions. In this case the active compound, which could not have a four-membered ring structure of the type (VII), was transformed into the inactive form with unusual facility in the presence of alkali, and the method of isolation had to be modified.

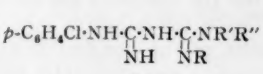
N^1-*p*-Chlorophenyl-N^2N^2-dimethyldiguanide (XI) did not condense with acetone, under either acidic or basic conditions. The failure to form an inactive isomer of type (II) was to be expected, but the failure to condense under acid conditions was surprising. The diguanide itself had certain unusual properties, as, for example, its high melting point and its low solubility in ether.

N^1-*p*-Chlorophenyl-N^4N^5-dimethyldiguanide (X; R = R′ = Me, R″ = H), with a basic catalyst, gave no condensation product that could be isolated. After a long reaction time under acid conditions there was obtained a small amount of the picrate of an ether-soluble base, which from its ultra-violet absorption spectrum and its stability to alkali appeared to have the structure (XII). Had a compound of the active type been formed, then the possibility of the metabolite's having a Schiff's base structure (VI) would have been elimin-

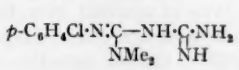
ated. In view of the difficulties experienced with this diguanide, it was not surprising that N^1-*p*-chlorophenyl-$N^2N^4N^5$-trimethyldiguanide did not condense with acetone under either basic or acidic conditions.



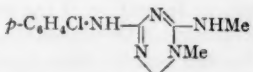
(IX)



(X)



(XI)



(XII)

The results obtained with N^1N^2-disubstituted diguanides were of great interest. With N^1-*p*-chlorophenyl-N^2-methyldiguanide (IV; X = Cl, R = H, R′ = Me) two products were obtained by the usual procedures. When however the isomerisation of the compound from the acid-catalysed condensation (IX; X = Cl, R = Me·NH, R′ = H) was studied, the ultra-violet absorption spectrum of the product suggested that it was an equilibrium mixture of the two isomeric forms, and this view was strengthened when it was found that caustic alkali-treatment of the base-catalysed condensation product (V; X = Cl, R = H, R′ = Me, R″ = NH_2) gave a similar mixture. The absorption spectrum of the equilibrium mixture indicated that it contained between three and four parts of the inactive to one part of the active isomer (see Fig. 2). Owing to the similar solubility of the two bases in ether the components of the mixture could not readily be separated in the usual way, but the mixed hydrochlorides were separated by counter-current distribution between water and butanol. The two fractions were again characterised by their absorption spectra.

Apart from the structural implications, these results with N^1-*p*-chlorophenyl-N^2-methyldiguanide show that the two types of condensation with acetone are quite distinct. If the reaction in the presence of piperidine had first given the aryl-dihydrotriazine which then, under the basic conditions obtaining, had rearranged to give the anilino-dihydrotriazine a mixture of the two would have been expected. Since however the anilino-compound was isolated readily in a pure state its formation must have been independent of that of its isomer. The formation of the *N*-methylanilino-type (V; R = Me, R′ = H, R″ = NH_2) from N^1-aryl-N^1-methyldiguanides mentioned above, which cannot proceed by way of an aryldihydrotriazine, bears out this conclusion.

N^1N^2-Di-*p*-chlorophenyldiguanide (IV; X = Cl, R = H, R′ = *p*-C_6H_4Cl), when condensed with acetone under either acidic or basic conditions, gave one and the same product. This was stable to alkali, the absence of any isomerisation being shown clearly by the ultra-violet absorption characteristics. A similar result was obtained with N^1N^2-diphenyldiguanide (IV; X = R = H, R′ = Ph).

The results with these N^1N^2-disubstituted diguanides gave the only positive evidence of structure obtained from the experiments on the condensation reactions of polysubstituted diguanides. Since members of the inactive series have already been shown to have the dihydrotriazine structure (II), the only ready explanation of the equilibrium between the two isomers in the condensation of N^1-*p*-chlorophenyl-N^2-methyldiguanide with acetone is found in the formulation of both as dihydrotriazine derivatives. Again, the failure to obtain, from the two N^1N^2-diaryldiguanides, isomers unstable to alkali indicated that acidic conditions for the condensation led directly to dihydrotriazines, which, in this case, were necessarily identical with those formed under basic conditions.

Attempts to synthesise the active metabolite by methods which would provide an unambiguous proof of structure have been unsuccessful. For example, the direct addition of dicyandiamide to compounds of the acetone anil type, would, if it gave compounds of the active type, be some confirmation of the triazine structure. The Schiff's bases from ketones and aromatic amines are not very well-characterised substances, and therefore the reaction between benzylideneaniline and dicyandiamide was chosen for study. In the absence of acid no reaction was observed, but, with acid present, a small yield of 4 : 6-

diamino-1 : 2-dihydro-1 : 2-diphenyl-1 : 3 : 5-triazine was obtained, identical with the product isolated from the condensation of phenyldiguanide with benzaldehyde in the presence of acid. Unfortunately, the Schiff's base itself is hydrolysed to its components under acid conditions, so that the synthesis has no real structural significance.

To sum up the evidence, the failure to form a copper complex, the halogenation experiments, and the results of the condensations of the N^1N^2-disubstituted diguanides, all favour the dihydrotriazine structure (III) for the active metabolite. Against this must be put the failure to resolve the condensation products with aldehydes or unsymmetrical ketones, and perhaps the formation of the inactive type of product from the acid condensation of N^1-*p*-chlorophenyl-N^4N^5-dimethyldiguanide and acetone. These results would best be explained by the Schiff's base structure (VI). On balance the evidence is considered to favour the structure (III), and this has been established beyond doubt by the *X*-ray crystallographic studies of Miss M. Bailey (*Acta Cryst.*, 1954, in the press).

Experimental

Rearrangement of **4 : 6-*Diamino*-1-p-*chlorophenyl*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine*** (III; R = R′ = Me).—**4 : 6-Diamino-1-*p*-chlorophenyl-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine** (crude base prepared from crude picrate isolated from the urine of rabbits dosed with proguanil) (Crowther and Levi, *loc. cit.*) (0·128 g.) was dissolved in warm water (4 c.c.). The solution was boiled for about 2 min., filtered whilst hot, and cooled. The colourless elongated parallelepipeds which separated were collected, washed with water, and dried; they had m. p. 135°, undepressed on admixture with 4-amino-6-*p*-chloroanilino-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine hydrate (Birtwell *et al.*, *loc. cit.*). Ultra-violet absorption in 0·00[illegible]-HCl: $\lambda_{max.}$ 255 mμ (ε 16,900). The picrate was prepared from aqueous solution and recrystallised from ethanol as orange-yellow needles, m. p. 233—235° undepressed on admixture with the picrate described below.

4-*Amino*-6-p-*chloroanilino*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine* (II; R = R′ = Me).—This was prepared from *p*-chlorophenyldiguanide, acetone, and piperidine (*idem, ibid.*). Ultra-violet absorption: in 0·01N-HCl, $\lambda_{max.}$ 255 mμ (ε 16,600) (see Fig. 1); in 0·005N-HCl, $\lambda_{max.}$ 255 mμ (ε 17,500); in 0·1N-NaOH, $\lambda_{max.}$ 258 mμ (ε 17,200). The picrate, prepared in water and crystallised from ethanol, formed orange-yellow needles, m. p. 236—237° (Found: C, 42·3; H, 3·7; N, 23·3; Cl, 7·35. Calc. for $C_{11}H_{14}N_5Cl,C_6H_3O_7N_3$: C, 42·5; H, 3·5; N, 23·3; Cl, 7·4%). Crounse (*J. Org. Chem.*, 1951, **16**, 492) gives m. p. 238°.

4 : 6-*Diamino*-1-p-*chlorophenyl*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine* (III; R = R′ = Me).—(*a*) *p*-Chlorophenyldiguanide hydrochloride (100 g.), acetone (500 c.c.), and water (1 l.) were heated together under reflux for 15 hr. and then evaporated to 500 c.c. under reduced pressure and cooled. The crystals which separated were filtered off and the filtrate was stirred vigorously at 0—5° with ether (1 l.) whilst 10N-sodium hydroxide (100 c.c.) was added. The aqueous layer was separated and extracted with further amounts of ether until a test portion no longer gave a precipitate on the addition of ammonia and copper sulphate solution. The solution was neutralised with hydrochloric acid, and saturated aqueous picric acid was added. The picrate was collected, washed with water, and dried (0·6—1·2 g.). It crystallised from ethanol in long pale yellow needles, m. p. 209—210° undepressed on admixture with the picrate of the proguanil metabolite (Crowther and Levi, *loc. cit.*) (Found: C, 42·5; H, 3·8; N, 23·0. Calc. for $C_{11}H_{14}N_5Cl,C_6H_3O_7N_3$: C, 42·5; H, 3·5; N, 23·3%). A mixture of the picrate (171 mg.), water (5 c.c.), and hydrochloric acid (1 c.c.; *d* 1·18) was extracted exhaustively with ether. 40% Sodium hydroxide solution was then added to the aqueous solution until there was no further precipitation. The base was collected, washed with ice-cold water, and dried in a vacuum over sodium hydroxide flakes (yield 51 mg.; m. p. 145—146°). The crude base was dissolved, at room temperature, in chloroform (previously saturated with water) (4 c.c.). Ether (4 c.c.) was added to precipitate the pure base as colourless prisms, m. p. 146° (Found: N, 27·9. Calc. for $C_{11}H_{14}N_5Cl$: N, 27·8%). Ultra-violet absorption in 0·01N-HCl: $\lambda_{max.}$ 240 mμ (ε 12,300).

The pure base (0·5 g.) was heated under reflux with water (20 c.c.) (pH of solution, 8—9) for 2 hr., and then cooled. The isomer which separated was collected, washed with water, and dried (0·47 g.); it had m. p. 140—141° undepressed in admixture with (II; R = R′ = Me). Ultra-violet absorption: in 0·01N-HCl, $\lambda_{max.}$ 256 mμ (ε 16,900); in 0·1N-NaOH, $\lambda_{max.}$ 258 mμ (ε 17,400).

(*b*) *p*-Chlorophenyldiguanide hydrochloride (20 g.), water (200 c.c.), acetone (100 c.c.), and

hydrochloric acid (7·04 c.c., 1 equiv.; *d* 1·18) were heated together under reflux for 20 hr. The solution was evaporated to half its volume under reduced pressure and cooled. The solid which separated was removed and the filtrate was stirred at 0—5° with ether (200 c.c.) whilst 40% sodium hydroxide solution (30 c.c.) was added. The colourless solid thus precipitated was collected, washed with ether, and dried (9·8 g.). A portion of this crude base was crystallised as in (*a*) and then had m. p. 143° undepressed on admixture with pure base from (*a*). A further portion of the crude base was suspended in ethanol, and concentrated hydrochloric acid was added until the base had dissolved. The solution was filtered from a little solid, and ether was added to the filtrate. The precipitated *hydrochloride* was collected, washed with ether, dried, and crystallised from ethanol–ether or water, in prisms; the m. p. varied from 204° to 219° depending on rate of heating (Found: C, 45·75; H, 5·4; N, 23·9. $C_{11}H_{14}N_5Cl$,HCl requires C, 45·8; H, 5·2; N, 24·3%). Ultra-violet absorption in 0·01N-HCl: $\lambda_{max.}$ 240 mμ (ε 12,300). The hydrochloride of (III; R = R′ = Me) was more conveniently prepared by dissolution of the crude base in 7% hydrochloric acid, followed by neutralisation with ammonia. The hydrochloride then usually separated; otherwise, the addition of saturated salt solution caused its precipitation.

The *hydrobromide* was prepared similarly from the base and dilute hydrobromic acid. It formed prisms (from water), m. p. 213—214° (Found: C, 40·2; H, 4·8; N, 21·2. $C_{11}H_{14}N_5Cl$,HBr requires C, 39·7; H, 4·5; N, 21·1%).

The yield of (III; R = R′ = Me) was increased by lowering the reaction temperature to 50°. Prolonged reaction at room temperature also gave a good yield. Variation of the amount of additional hydrochloric acid either to 0·1 equiv. or to 2·0 equivs. had little effect, but reduction in the amount of acetone used, to slightly more than the stoicheiometric proportion, resulted in inferior yields. *p*-Chlorophenyldiguanide, acetone, and water, with either sulphuric acid or hydrobromic acid in amounts in excess of 1 equiv., gave good yields of (III; R = R′ = Me). Treatment with acetone and hydrochloric acid of the mixture obtained by heating *p*-chloroaniline hydrochloride with dicyandiamide in water, without the diguanide initially formed being isolated, gave the same compound. It was also formed from *p*-chloroaniline hydrochloride, dicyandiamide, acetone, and hydrochloric acid on being heated together in water. Acetone diethyl acetal and *iso*propenyl acetate each gave (III; R = R′ = Me)) on reaction with *p*-chlorophenyldiguanide hydrochloride and hydrochloric acid, as did acetone–sodium hydrogen sulphite, but in this case only in the presence of a considerable excess of acid.

Acid Hydrolysis of 4 : 6-*Diamino*-1-p-*chlorophenyl*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine* (III; R = R′ = Me).—The diamino-dihydrotriazine hydrochloride (5 g.) and 0·1N-hydrochloric acid (50 c.c.) were heated together under reflux for 30 min. The solution was evaporated to dryness under reduced pressure, leaving a crystalline residue (4·21 g.), which was crystallised from water, giving *p*-chlorophenyldiguanide hydrochloride, m. p. 239° undepressed on admixture with authentic material. The constitution of the hydrolysis product was confirmed by the formation of a water-insoluble complex on treatment with ammoniacal copper sulphate solution.

Prolonged heating of the diamino-dihydrotrizine with 7% hydrochloric acid gave *p*-chloroaniline in 75% yield.

N^1-p-*Chlorophenyl*-N^1-*methyldiguanide* (IV; X = Cl, R = Me, R′ = H).—*p*-Chloro-*N*-methylaniline hydrochloride (17·8 g.), dicyandiamide (10·6 g.), and water (35 c.c.) were heated together under reflux for 90 min. The cooled mixture was extracted with ether to remove unchanged base, carbon was added, and the mixture was filtered. The filtrate was made strongly alkaline with 40% sodium hydroxide solution, and the precipitated base was collected, washed with ice-cold water, and dried. Crystallisation from chlorobenzene gave N^1-p-*chlorophenyl*-N^1-*methyldiguanide* as colourless crystals, m. p. 156° (Found: C, 48·05; H, 5·3; N, 30·45. $C_9H_{12}N_5Cl$ requires C, 47·9; H, 5·3; N, 31·0%).

4-*Amino*-6-(p-*chloro*-N-*methylanilino*)-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine* (V; X = Cl, R = Me, R′ = H, R″ = NH_2).—(*a*) N^1-*p*-Chlorophenyl-N^1-methyldiguanide (3 g.), acetone (50 c.c.), and piperidine (0·3 c.c.) were heated together under reflux for 7 days. Water (100 c.c.) was added to the cooled mixture and the whole was made alkaline by the addition of ammonia. An excess of copper sulphate solution, to precipitate unchanged diguanide as the copper complex, was added. The mixture was filtered, the filtrate was acidified with hydrochloric acid, and sodium sulphide was added until there was no further separation of copper sulphide. Carbon was added and the mixture was filtered. Aqueous picric acid was added to the filtrate, and the *picrate* of the product was collected, washed with water, and dried (2·3 g.). It crystallised from ethanol in yellow platelets, m. p. 278° (Found: C, 43·25; H, 4·15; N, 22·45. $C_{12}H_{16}N_5Cl$,$C_6H_3O_7N_3$ requires C, 43·7; H, 3·85; N, 22·65%). The crude picrate was suspended in dilute hydrochloric acid and extracted with ether. The aqueous part was evaporated to dry-

ness under reduced pressure, and the residue was triturated with acetone, collected, washed with acetone and dried. The product crystallised from ethanol–ether, to give *4-amino-6-(p-chloro-N-methylanilino)-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine dihydrochloride*, m. p. 146—147° (Found: C, 39·3, 39·1; H, 5·95, 6·0; N, 19·6. $C_{12}H_{16}N_5Cl,2HCl,1·5H_2O$ requires C, 39·4; H, 5·7; N, 19·2%). Ultra-violet absorption: in 0·01N-HCl, $\lambda_{max.}$ 247·5 mμ (ε 16,300) (see Fig. 1); in 0·1N-NaOH, $\lambda_{max.}$ 260 mμ (ε 12,400).

(*b*) N^1-*p*-Chlorophenyl-N^1-methyldiguanide (3 g.), water (10 c.c.), acetone (5 c.c.), and hydrochloric acid (2·34 c.c.; *d* 1·18) were heated together under reflux for 16 hr. The solution was cooled, and basified with ammonia, and the small amount of oil which separated was removed by extraction with ether. The aqueous part was made strongly alkaline with 40% sodium hydroxide solution, and the solid precipitated was collected, dissolved in water, and filtered. Ammoniacal copper sulphate solution was added to the filtrate. The copper complex of the unchanged diguanide was filtered off, the filtrate was acidified with hydrochloric acid, and sodium sulphide was added. The precipitate was removed, the solution was neutralised with ammonia, and aqueous picric acid was added. The picrate thus formed was collected, washed with water, dried, and crystallised from ethanol, yielding pale yellow platelets, m. p. 275—276° undepressed in admixture with the picrate from (*a*).

N^1-*Methyl*-N^1-*phenyldiguanide* (IV; X = R′ = H, R = Me).—*N*-Methylaniline (53·5 g.), hydrochloric acid (43·7 c.c.; *d* 1·18), dicyandiamide (41·5 g.), and water were heated together under reflux for 1·5 hr. and then filtered after addition of carbon. The cooled filtrate was treated with sodium hydroxide solution, and the precipitated base was collected, washed with water, dried (H_2SO_4; vac.), and crystallised from benzene. The base could not be further purified but was sufficiently pure for the reaction below. It was characterised as the *hydrochloride*, colourless needles, m. p. 205°, from ethanol–ethyl acetate (Found: N, 30·55. $C_9H_{13}N_5,HCl$ requires N, 30·8%), and as the *picrate*, yellow platelets, m. p. 170—171°, from ethanol (Found: C, 43·25; H, 3·9; N, 27·65, 27·85. $C_9H_{13}N_5,C_6H_3O_7N_3$ requires C, 42·9; H, 3·8; N, 26·7%). Satisfactory nitrogen analyses could not be obtained. Cohn (*J. pr. Chem.*, 1911, **84**, 394) described this preparation but did not characterise the product.

4-Amino-1 : 2-dihydro-2 : 2-dimethyl-6-(N-methylanilino)-1 : 3 : 5-triazine (V; X = R′ = H, R = Me, R″ = NH_2).—N^1-Methyl-N^1-phenyldiguanide (12 g.), dry acetone (50 c.c.), and piperidine (1 c.c.) were heated together under reflux for 22 hr. The solution was filtered, and evaporated under reduced pressure. The syrupy residue was dissolved in water, and aqueous picric acid was added. The *picrate* thus precipitated was collected, washed with water, dried, and crystallised from ethanol; it had m. p. 239—240° (Found: C, 47·05; H, 4·5; N, 23·95. $C_{12}H_{17}N_5,C_6H_3O_7N_3$ requires C, 46·95; H, 4·35; N, 24·3%). In order to measure the ultra-violet absorption of the product, a portion of the picrate was shaken with dilute hydrochloric acid and ether, and the aqueous part examined. Ultra-violet absorption: in 0·01N-HCl, λ_{max} 247 mμ (ε 15,600); in 0·1N-NaOH, $\lambda_{max.}$ 255 mμ (ε 12,000).

4 : 6-Diamino-1 : 2-dihydro-2 : 2-dimethyl-1-phenyl-1 : 3 : 5-triazine (IX; X = R′ = H, R = NH_2).—(*a*) Phenyldiguanide (35 g.), acetone (200 c.c.), and hydrochloric acid (34 c.c.; *d* 1·18) were heated in water (400 c.c.) under reflux on the steam-bath for 15 hr. The acetone was distilled off under reduced pressure, and the mixture was cooled to 3°. Ether (500 c.c.) was added, and the mixture was made strongly alkaline with 40% sodium hydroxide solution and shaken. The ethereal layer was decanted and a second ether-extraction was carried out. The residue was filtered and the solid was washed with ether and dried *in vacuo* (36 g.). Crystallisation from moist chloroform by addition of ether and light petroleum gave the *base*, m. p. 138—139° (Found: C, 56·2; H, 6·7; N, 29·4. $C_{11}H_{15}N_5,H_2O$ requires C, 56·2; H, 7·2; N, 29·8%). The base was dissolved in ethanol and concentrated hydrochloric acid, and ether was added until crystallisation of the *hydrochloride* occurred. Recrystallised from ethanol–ether, it formed colourless needles, m. p. 209—210° (Found: C, 50·05; H, 5·9; N, 26·3. $C_{11}H_{15}N_5,HCl,0·5H_2O$ requires C, 50·25; H, 6·45; N, 26·7%). Ultra-violet absorption in 0·01N-HCl: $\lambda_{max.}$ 240 mμ (ε 7400).

(*b*) The dihydrotriazine was also conveniently prepared from aniline hydrochloride and dicyandiamide, with a subsequent similar reaction with acetone, without the isolation of phenyldiguanide hydrochloride.

4-Amino-6-anilino-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine (V; X = R = R′ = H, R″ = NH_2).—4 : 6-Diamino-1 : 2-dihydro-2 : 2-dimethyl-1-phenyl-1 : 3 : 5-triazine (3 g.), 40% sodium hydroxide solution (1 c.c.), and water (100 c.c.) were heated together on the steam-bath for 45 min. The solution was cooled, and 40% sodium hydroxide solution was added to precipitate a gum which crystallised on trituration with ethanol. The *base* crystallised from water,

m. p. 184—185° (Found: C, 61·4; H, 7·05; N, 32·0. $C_{11}H_{15}N_5$ requires C, 60·8; H, 6·9; N, 32·3%). Ultra-violet absorption: in 0·01N-HCl, $\lambda_{max.}$ 250 mμ (ε 14,800); in 0·1N-NaOH, $\lambda_{max.}$ 253 mμ (ε 15,100).

4 : 6-*Diamino*-1-p-*chlorophenyl*-2-*ethyl*-1 : 2-*dihydro*-2-*methyl*-1 : 3 : 5-*triazine* (III; R = Me, R′ = Et).—*p*-Chlorophenyldiguanide hydrochloride (37 g.), ethyl methyl ketone (100 c.c.), and hydrochloric acid (12·9 c.c.; *d* 1·18) in water (200 c.c.) were kept at 70° for 15 hr. The unchanged ketone was distilled off under reduced pressure. The residue was cooled to 3°, ether (200 c.c.) was added, and the mixture was made strongly alkaline with 40% sodium hydroxide solution. The ethereal layer was separated, the aqueous suspension was extracted twice more with ether, and the solid product was separated by filtration. It was washed with water, and dried *in vacuo* (24 g.). Recrystallisation by addition of ether and light petroleum (b. p. 60—80°) to a solution in moist chloroform gave **4 : 6-*diamino*-1-p-*chlorophenyl*-2-*ethyl*-1 : 2-*dihydro*-2-*methyl*-1 : 3 : 5-*triazine*** as prisms, m. p. 139—140° (Found: C, 54·35; H, 6·45; N, 26·5. $C_{12}H_{16}N_5Cl$ requires C, 54·2; H, 6·05; N, 26·4%). Ultra-violet absorption in 0·01 N-HCl: $\lambda_{max.}$ 242 mμ (ε 11,600). Addition of ether to a solution of the base in ethanolic hydrogen chloride yielded the ***hydrochloride***, needles (from ethanol–ether), m. p. 206—208° (Found: C, 48·0; H, 5·65; N, 22·9. $C_{12}H_{16}N_5Cl,HCl$ requires C, 47·7; H, 5·65; N, 23·2%).

The (+)-***tartrate*** was prepared from the base (30 g.) and (+)-tartaric acid (16·9 g.) in ethanol (200 c.c.). The solution was filtered and evaporated under reduced pressure to a syrup, which crystallised on trituration with methanol and acetone (34 g.). After two recrystallisations from aqueous ethanol, the tartrate had m. p. 186—187° [Found: C, 49·5; H, 5·6; N, 20·25. $(C_{12}H_{16}N_5Cl)_2,C_4H_6O_6$ requires C, 49·3; H, 5·6; N, 20·6%], $[\alpha]_D^{20}$ + 4·2° (*c*, 5 in H_2O). Repeated crystallisation failed to effect resolution of this salt, and the base recovered from it was optically inactive.

4-*Amino*-6-p-*chloroanilino*-2-*ethyl*-1 : 2-*dihydro*-2-*methyl*-1 : 3 : 5-*triazine* (II; R = Me, R′ = Et).—**4 : 6-Diamino-1-*p*-chlorophenyl-2-ethyl-1 : 2-dihydro-2-methyl-1 : 3 : 5-triazine** (10 g.) was suspended in water (100 c.c.), heated on the steam-bath for 1 hr., and then cooled. The oil, after being separated from the supernatant liquid, solidified. It was recrystallised twice from aqueous methanol, to give **4-*amino*-6-p-*chloroanilino*-2-*ethyl*-1 : 2-*dihydro*-2-*methyl*-1 : 3 : 5-*triazine***, plates, m. p. 140—142° (Found: C, 52·0; H, 6·3; N, 25·8. $C_{12}H_{16}N_5Cl,0·5H_2O$ requires C, 52·0; H, 6·2; N, 25·5%). Ultra-violet absorption in 0·1N-NaOH: $\lambda_{max.}$ 258 mμ (ε 17,700).

Resolution of **4-*Amino*-6-p-*chloroanilino*-2-*ethyl*-1 : 2-*dihydro*-2-*methyl*-1 : 3 : 5-*triazine***.—The above base (12 g.) was suspended in ethanol (25 c.c.), and a solution of (+)-tartaric acid (7·5 g.) in ethanol (25 c.c.) was added. The mixture was heated to 40° and the solution thus obtained was filtered and evaporated to half-bulk under reduced pressure. The solution was kept overnight at 0° and the crystals which separated were collected (5·7 g.), m. p. 80—82°. After two recrystallisations from ethanol the tartrate had m. p. 82—83°. The product, which was highly solvated, lost readily only part of its ethanol of crystallisation in air (Found, on material dried at 56° *in vacuo* over P_2O_5: C, 46·4; H, 6·4; N, 14·6. $C_{12}H_{16}N_5Cl,C_4H_6O_6,C_2H_5OH$ requires C, 46·8; H, 6·1; N, 15·2%), $[\alpha]_D^{20}$ +74° (*c*, 5 in H_2O). A solution of the tartrate in water was made strongly alkaline by addition of sodium hydroxide solution. The precipitated dextrorotatory ***base*** formed plates, m. p. 120—121°, from ethanol (Found: C, 53·8; H, 7·0; N, 22·5. $C_{12}H_{16}N_5Cl,C_2H_5OH$ requires C, 53·9; H, 7·05; N, 22·5%), $[\alpha]_D^{23}$ +16° (*c*, 5 in EtOH).

Derivatives of **4-*Amino*-6-p-*chloroanilino*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine***.—**4-Amino-6-*p*-chloroanilino-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine** (II; R = R′ = Me) (4·05 g.), acetic anhydride (4 c.c.), and acetic acid (15 c.c.) were heated together under reflux for 1 hr. The mixture was then poured into water (100 c.c.) and cooled. The solid was collected, washed with water, dried, and crystallised from ethanol, giving the ***diacetyl*** derivative as hydrated colourless prisms, m. p. 214° (Found: C, 51·1; H, 5·45; N, 20·0; Cl, 10·2. $C_{15}H_{18}O_2N_5Cl,H_2O$ requires C, 51·0; H, 5·7; N, 19·8; Cl, 10·0%).

The 4-amino-triazine (1·35 g.) and *p*-chlorophenyl *iso*thiocyanate (2·54 g.) in acetone (30 c.c.) were heated under reflux for 3 hr. The solution was cooled, diluted with water (100 c.c.), and steam-distilled to remove excess of *iso*thiocyanate. The residue was filtered and the solid was washed with water and dried. It crystallised from ethanol to give colourless rods of the ***thiourea***, m. p. 199—200° (Found: C, 51·1; H, 4·15; N, 20·05, 20·2; S, 8·2. $C_{18}H_{18}N_6Cl_2S$ requires C, 51·3; H, 4·3; N, 19·95; S, 7·6%).

6-p-*Chloroanilino*-1 : 2-*dihydro*-4-*hydroxy*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine* (V; X = Cl, R = R′ = H, R″ = OH).—(*a*) **4-Amino-6-*p*-chloroanilino-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine** (2·5 g.) was warmed in 7% hydrochloric acid (20 c.c.) to 80°. Sodium nitrite solution (13·8 c.c.; 10%) was added during 30 min. and the mixture was kept at 80° for a further 10 min.

The solution was cooled, carbon was added, and the mixture was filtered. The filtrate was basified with 40% sodium hydroxide solution, and the liberated base was collected, washed with water, dried, and crystallised from ethanol, yielding fine colourless needles of the *hydroxy*-compound, m. p. 250° (decomp.) (Found: C, 52·45; H, 5·15; N, 22·35. $C_{11}H_{13}ON_4Cl$ requires C, 52·3; H, 5·15; N, 22·2%). The *hydrochloride* had m. p. 224° (effervescence), undepressed on admixture with the hydrochloride from (*b*) below; ultra-violet absorption: in 0·1N-HCl, $\lambda_{max.}$ 228—236 mμ (ε 10,500); in 0·1N-NaOH, $\lambda_{max.}$ 252—262 mμ (ε 15,500).

(*b*) *p*-Chlorophenyldicyandiamide (5 g.), *iso*propanol (12 c.c.), and hydrochloric acid (2·5 c.c.; *d* 1·18) were heated together under reflux for 30 min. A further amount of hydrochloric acid (1·5 c.c.) was then added and the heating was continued for a further 2 hr. The solution was poured into water (100 c.c.), and the solid precipitated was removed. The filtrate was basified with sodium hydroxide solution, and the base thus liberated was collected, washed with water, and dried. It crystallised from benzene containing a small amount of ethanol to give *p*-chlorophenylguanylurea of m. p. 133—134° (Found: N, 26·7. Calc. for $C_8H_9ON_4Cl$: N, 26·4%) (Walther and Griesshammer, *J. pr. Chem.*, 1915, **92**, 251, give m. p. 125°). *p*-Chlorophenylguanylurea (20 g.) and piperidine (2 c.c.) were heated in acetone (200 c.c.) under reflux for 20 hr. The solution was filtered, the filtrate was evaporated to dryness, and the syrupy residue was dissolved in ethanol and poured into water, to give a solid, which was collected, washed with water, and dried. It was dissolved in alcoholic hydrogen chloride, and ethyl acetate was added. The precipitate was collected, washed with ethyl acetate, and dried. Crystallisation from ethanol gave prisms of **6-p-*chloroanilino*-1 : 2-*dihydro*-4-*hydroxy*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine hydrochloride***, m. p. 223° (effervescence) (Found: C, 45·55; H, 4·75; N, 19·55. $C_{11}H_{13}ON_4Cl,HCl$ requires C, 45·7; H, 4·8; N, 19·4%). Ultra-violet absorption: in 0·1N-HCl, $\lambda_{max.}$ 226—236 mμ (ε 10,500); in 0·1N-NaOH, $\lambda_{max.}$ 257 mμ ε, 13,300).

N-p-*Chlorophenyl*-N′-*guanylurea*.—*p*-Chlorophenyldiguanide hydrochloride (5 g.) was stirred at room temperature in 7% hydrochloric acid (100 c.c.) whilst sodium nitrite (2 g.) was added. The mixture was kept at 20° for 1 hr. and then filtered. The solid residue was washed with a little water, drained, and dissolved in dilute hydrochloric acid. The solution was treated with carbon, filtered, and basified. The precipitate thus formed was collected, washed with water, and crystallised from water, to give *N*-*p*-chlorophenyl-*N*′-guanylurea as feathery needles, m. p. 140° (Found: C, 45·15; H, 4·4; N, 25·85. Calc. for $C_8H_9ON_4Cl$: C, 45·2; H, 4·2; N, 26·4%). Passerini (*Chem. Abs.*, 1951, **45**, 10208) since the completion of this work has reported m. p. 143°.

4-*Amino*-1-p-*chlorophenyl*-1 : 2-*dihydro*-6-*hydroxy*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine* (IX; X = Cl, R = OH, R′ = H).—*N*-*p*-Chlorophenyl-*N*′-guanylurea (10 g.) and piperidine (1·2 c.c.) were heated in acetone (65 c.c.) under reflux for 17 hr. The mixture was cooled and the solid was collected, washed with acetone, and dried. It crystallised from aqueous 2-ethoxyethanol as fine needles of the *dihydrotriazine*, m. p. 227° (decomp.) (Found: C, 52·25, 52·4; H, 5·4, 5·3; N, 21·7. $C_{11}H_{13}ON_4Cl$ requires C, 52·3; H, 5·15; N, 22·2%).

4 : 6-*Diamino*-1-p-*chlorophenyl*-1 : 2-*dihydro*-2-iso*propyl*-1 : 3 : 5-*triazine* (III; R = H, R′ = Pr^i).—*p*-Chlorophenyldiguanide hydrochloride (12·4 g.), *iso*butyraldehyde (50 c.c.), hydrochloric acid (4·3 c.c.; *d* 1·18), ethanol (20 c.c.), and water (100 c.c.) were heated together at 70° for 15 hr. The ethanol and excess of *iso*butyraldehyde were distilled under reduced pressure, and the residue was cooled to 3°. Ether (200 c.c.) was added, and the mixture was made strongly alkaline by addition of 40% sodium hydroxide solution. The solid product was separated by filtration, washed with ether and then with water, and dried *in vacuo* (15·2 g.), m. p. 144—146°. The base could not readily be recrystallised, but was dissolved in dilute aqueous hydrochloric acid, filtered, and then neutralised with ammonia; the *hydrochloride* separated as prisms, m. p. 226—227° (Found: C, 42·6; H, 6·2; N, 20·7. $C_{12}H_{16}N_5Cl,HCl,2H_2O$ requires C, 41·95; H, 5·8; N, 20·5%). Ultra-violet absorption in 0·01N-HCl: $\lambda_{max.}$ 244 mμ (ε 10,600). The (+)-*tartrate* was prepared from the crude base (20·5 g.) and (+)-tartaric acid (11·6 g.) in ethanol (120 c.c.). The solution was set aside and then filtered to remove a small amount of gelatinous material. Addition of ethyl acetate (50 c.c.) caused separation of the crystalline salt (18 g.), which, when recrystallised from aqueous ethanol, had m. p. 196—197°, $[\alpha]_D^{20}$ +9·6° (*c*, 5 in H_2O) [Found: C, 48·4; H, 5·3; N, 20·0. $(C_{12}H_{16}N_5Cl)_2,C_4H_6O_6,H_2O$ requires C, 48·3; H, 5·7; N, 20·2%]. Repeated crystallisation failed to bring about any resolution of this salt.

4-*Amino*-6-p-*chloroanilino*-1 : 2-*dihydro*-2-iso*propyl*-1 : 3 : 5-*triazine* (II; R = H, R′ = Pr^i).—The above hydrochloride (5 g.) was dissolved in hot water (100 c.c.), and the solution was made alkaline by addition of 40% sodium hydroxide solution. The mixture was heated on the steam-bath for 1 hr., and cooled. The gummy product was separated, and triturated with methanol. The solid obtained was crystallised from aqueous methanol, giving 4-*amino*-6-p-

chloroanilino-1 : 2-*dihydro*-2-iso*propyl*-1 : 3 : 5-*triazine* as a solvate (2·5 g.), m. p. 118—120° (Found : C, 52·4; H, 6·45; N, 22·8. $C_{12}H_{16}N_5Cl,CH_3{\cdot}OH$ requires C, 52·4; H, 6·7; N, 23·5%).

4 : 6-*Diamino*-1-p-*chlorophenyl*-2-*ethyl*-1 : 2-*dihydro*-1 : 3 : 5-*triazine* (III; R = H; R′ = Et).—*p*-Chlorophenyldiguanide hydrochloride (24·8 g.), propionaldehyde (25·6 g.), hydrochloric acid (8·73 c.c.; *d* 1·18), and water (75 c.c.) were stirred together at 50° for 17 hr. The cooled mixture was extracted with ether; the aqueous part was then stirred with ether (150 c.c.) at 0—5°, and sodium hydroxide solution was added until there was no further precipitation. The solid was collected, washed with ether, and dried. It was dissolved in dilute hydrochloric acid, the solution was filtered, and the filtrate was neutralised with aqueous ammonia. Saturated salt solution was added to complete precipitation and the solid was collected, washed with a little water, and dried. Crystallisation from water gave the *hydrochloride*, m. p. 244—245° (Found : C, 46·1; H, 5·3; N, 23·7. $C_{11}H_{14}N_5Cl,HCl$ requires C, 45·8; H, 5·2; N, 24·3%). Ultra-violet absorption in 0·01N-HCl : $\lambda_{max.}$ 244 mμ (ε 10,200). The crude base (6·06 g.) in ethanol (50 c.c.) was mixed with a solution of (+)-camphorsulphonic acid (5·65 g.) in ethanol (50 c.c.) at room temperature. The crystals which separated were collected, washed with ethanol, and dried (3·85 g.; m. p. 217°). The product was crystallised four times from ethanol (the optical rotation was unchanged) to give the (+)-*camphorsulphonate* as prisms, m. p. 217°, $[\alpha]_D^{20}$ + 19·8° (*c*, 2·22 in EtOH) (Found : C, 51·4; H, 6·3; N, 13·9; Cl, 7·0. $C_{11}H_{14}N_5Cl,C_{10}H_{16}O_4S,0{\cdot}5H_2O$ requires C, 51·2; H, 6·3; N, 14·2; Cl, 7·2%). The base recovered from the recrystallised salt was optically inactive.

4(or 6)-*Amino*-1-p-*chlorophenyl*-6(or 4)-p-*chlorophenylthioureido*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine*.—4 : 6-Diamino-1-*p*-chlorophenyl-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine (III; R = R′ = Me) (2·51 g.), *p*-chlorophenyl *iso*thiocyanate (5·08 g.), and acetone (100 c.c.) were heated together under reflux for 90 min. The solution was then evaporated to a small bulk and diluted with light petroleum (b. p. 60—80°) to precipitate an oil which readily crystallised. The solid was collected, washed with light petroleum (b. p. 60—80°), dried, and crystallised from ethanol to give the *thiourea*, m. p. 174—175° (Found : C, 51·05; H, 4·45; N, 19·35; S, 7·55. $C_{18}H_{18}N_6Cl_2S$ requires C, 51·3; H, 4·3; N, 19·95; S, 7·6%).

Chlorination of 4-*Amino*-6-*anilino*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine* (V; X = R = R′ = H, R″ = NH_2).—The anilino-dihydrotriazine (13·96 g.) was dissolved in acetic acid (90 c.c.), and chlorine (4·86 g.) was passed into the solution at 20° during 20 min. Addition of ether precipitated a gum which was separated, washed with ether, dissolved in water and basified with sodium hydroxide solution. The precipitated gummy base was converted into the picrate which crystallised from ethanol as orange-yellow needles of 4-amino-6-*p*-chloroanilino-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine picrate of m. p. 236—237° undepressed on admixture with authentic material.

6-*Amino*-1-p-*chlorophenyl*-4-*dimethylamino*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine* (IX; X = Cl, R = NH_2, R′ = Me).—A mixture of N^1-*p*-chlorophenyl-N^5N^5-dimethyldiguanide hydrochloride hemihydrate (22·8 g.), acetone (200 c.c.), and 7% hydrochloric acid (40 c.c.) was heated under reflux for 18 hr. on a steam-bath. The solution was concentrated (to about 40 c.c.) below 50° and 7% aqueous ammonia was added to give a pH of 5. Addition of saturated aqueous sodium chloride (about 140 c.c.) to the filtered solution gave a gum which later solidified and was collected, dissolved in water (25 c.c.), and filtered. The filtrate was again treated with sufficient saturated aqueous sodium chloride to give a permanent turbidity. The solution was cooled in ice-water, the crystals obtained were collected and dissolved in ethanol (45 c.c.), and the clarified solution was mixed with ethyl acetate (250 c.c.) and ethanolic 16% hydrogen chloride (8 c.c.). The precipitated *dihydrochloride* was purified by dissolution in ethanol, and addition of an excess of ethyl acetate containing a little ethanolic hydrogen chloride. The small prisms thus obtained melted at 186—188°, resolidified almost at once, and remelted at 264·5° (Found : C, 43·85; H, 5·35; N, 20·1. $C_{13}H_{18}N_5Cl,2HCl$ requires C, 44·2; H, 5·7; N, 19·85%).

The crude dihydrochloride (7·5 g.) was dissolved in water (18 c.c.), the pH of the solution was adjusted to 5 with aqueous ammonia (*d* 0·88), and saturated aqueous sodium chloride (15 c.c.) was added, to give the *monohydrochloride*, prisms (from ethanol–ether), m. p., after previous melting at 120° and resolidification, 263—264°, not depressed by the isomeric hydrochloride below (Found : C, 48·45; H, 6·6; N, 21·35. $C_{13}H_{18}N_5Cl,HCl,0{\cdot}5H_2O$ requires C, 48·05; H, 6·2; N, 21·6%). Ultra-violet absorption : in 0·01N-HCl, $\lambda_{max.}$ 246 mμ (ε 22,300); in 0·1N-NaOH, $\lambda_{max.}$ 243 mμ (ε 17,000). The *hydriodide* was slightly less soluble than the hydrochloride in water. It formed small colourless rods which melted in the region of 110° and decomposed about 145° (Found : C, 36·85; H, 5·25; N, 16·2; loss in wt. in vacuum at

80°, 3·65. $C_{13}H_{18}N_5Cl,HI,H_2O$ requires C, 36·5; H, 4·95; N, 16·4; H_2O, 4·2%). The *picrate* crystallised as yellow prisms from ethanol. When heated fairly rapidly, it melted partially at about 180°, resolidified, and melted finally at 242—243° (Found : C, 45·3; H, 4·3; N, 21·9. $C_{13}H_{18}N_5Cl,C_6H_3O_7N_3$ requires C, 44·9; H, 4·15; N, 22·0%).

6-p-*Chloroanilino*-4-*dimethylamino*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine* (V; X = Cl, R = R′ = H, R″ = NMe_2).—N^1-*p*-Chlorophenyl-N^5N^5-dimethyldiguanide (14·5 g.), acetone (60 c.c.), and piperidine (0·8 c.c.) were heated under reflux for 76 hr. The liquid was cooled, concentrated (to about 25 c.c.), and mixed with water (50 c.c.). Unchanged diguanide was filtered off, and the mother-liquors were freed from acetone by distillation under reduced pressure and acidified with 7% hydrochloric acid. The solid (4·0 g.) which separated was collected, and crystallised from dilute hydrochloric acid to give 6-p-*chloroanilino*-4-*dimethylamino*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine hydrochloride* as needles, m. p. 265—266° (Found : C, 49·25; H, 5·85; N, 21·8. $C_{13}H_{18}N_5Cl,HCl$ requires C, 49·3; H, 6·05; N, 22·1%). Ultra-violet absorption : in 0·01N-HCl, $\lambda_{max.}$ 259 mμ (ε 19,800); in 0·1N-NaOH, $\lambda_{max.}$ 262 mμ (ε 21,500). The *picrate* crystallised from 2-ethoxyethanol as blunt yellow needles, m. p. 241—242° (Found : C, 45·05; H, 4·0; N, 21·5. $C_{13}H_{18}N_5Cl,C_6H_3O_7N_3$ requires C, 44·9; H, 4·15; N, 22·0%). Unlike the isomeric picrate described above, this compound showed no tendency to melt at about 180°.

N^1-p-*Chlorophenyl*-N^2N^2-*dimethyldiguanide* (XI).—This was prepared from *N*-*p*-chlorophenyl-*N*′-guanylthiourea (11·4 g.), aqueous dimethylamine (45 c.c. ; 25%), ethanol (500 c.c.), and mercuric oxide (32·5 g.), stirred together for 15 hr. at room temperature. The filtered solution was evaporated under reduced pressure, and the residue, crystallised from aqueous ethanol, gave N^1-p-*chlorophenyl*-N^2N^2-*dimethyldiguanide*, m. p. 227° (decomp.) (Found : C, 49·9; H, 5·55; N, 29·3. $C_{10}H_{14}N_5Cl$ requires C, 50·2%; H, 5·85; N, 29·2%).

Reaction between N^1-p-*Chlorophenyl*-N^4N^5-*dimethyldiguanide and Acetone under Acidic Conditions.*—N^1-*p*-Chlorophenyl-N^4N^5-dimethyldiguanide hydrochloride (4·15 g.), 3·5% hydrochloric acid (15 c.c.), water (22 c.c.), and acetone (22 c.c.) were heated together for 70 hr. in a water-bath at 70°. The solution was concentrated (to about 30 c.c.) at 50°, cooled, mixed with ether (50 c.c.), and kept at 0—5° while an excess of aqueous 40% sodium hydroxide was added. The ethereal solution, combined with a second extract of the aqueous layer, was dried (Na_2SO_4). Removal of the ether left a solid which was dissolved in ethanol and treated with an excess of picric acid. The product (2·65 g.) was recrystallised from *n*-propanol and dried at 110°/20 mm., to give yellow 4-p-*chloroanilino*-1 : 2-*dihydro*-1 : 2 : 2-*trimethyl*-6-*methylamino*-1 : 3 : 5-*triazine picrate* (as XII), which melted partially at 168—169°, then resolidified, and later melted at 184—185° (Found : C, 45·4; H, 4·0; N, 21·8; $C_{13}H_{18}N_5Cl,C_6H_3O_7N_3$ requires C, 44·9; H, 4·15; N, 22·0%). The *base*, prepared from the picrate and crystallised from benzene and dried at 100°/20 mm., had m. p. 126—127° (Found : C, 55·3; H, 6·5; N, 24·5. $C_{13}H_{18}N_5Cl$ requires C, 55·8; H, 6·5; N, 25·1%). Ultra-violet absorption : in 0·01N-HCl, $\lambda_{max.}$ 265 mμ (ε 18,500); in 0·1N-NaOH, $\lambda_{max.}$ 265 mμ (ε 21,200).

N-(N-p-*Chlorophenyl*-N′-*methylguanyl*)-N′-*methylthiourea.*—*N*-*p*-Chlorophenyl-*N*′-methylguanidine (34 g.) and methyl *iso*thiocyanate (14·6 g.) were heated together on the steam-bath for 4 hr. The mixture was steam-distilled and the water was decanted from the residue which was then dissolved in hot ethanol (30 c.c.), treated with carbon, and filtered. The filtrate was stirred vigorously while 10% hydrochloric acid (100 c.c.) was slowly added. The precipitate was filtered off, washed with acetone, and dried. Recrystallisation from 85% methanol (carbon) gave N-(N-p-*chlorophenyl*-N′-*methylguanyl*)-N′-*methylthiourea hydrochloride* as colourless rectangular prisms (12·2 g.), m. p. 190—191° (decomp.) (Found : C, 41·1; H, 5·2; N, 18·75. $C_{10}H_{13}N_4ClS,HCl$ requires C, 41·0; H, 4·8; N, 19·15%).

N^1-p-*Chlorophenyl*-$N^2N^4N^5$-*trimethyldiguanide.*—A mixture of *N*-(*N*-*p*-chlorophenyl-*N*′-methylguanyl)-*N*′-methylthiourea hydrochloride (20·5 g.), aqueous methylamine (57 c.c. ; 23% solution), mercuric oxide (45·4 g.), and ethanol (400 c.c.) was stirred at 30—40° for 16 hr., then heated on the steam-bath for 30 min. and filtered. The filtrate was evaporated to dryness under reduced pressure and the residual gum was dissolved in 7% hydrochloric acid (100 c.c.). The solution was clarified and an excess of aqueous 40% sodium hydroxide was added, to precipitate a sticky solid which was extracted with ether. The residue left after removal of the ether was redissolved in 7% hydrochloric acid (50 c.c.), and aqueous ammonia (*d* 0·88) was added to give a pH of 5. Addition of saturated aqueous sodium chloride to the carbon-treated solution caused precipitation of N^1-p-*chlorophenyl*-$N^2N^4N^5$-*trimethyldiguanide hydrochloride* (60%), m. p. 201—202°. Recrystallised from ethanol–ethyl acetate, it formed prisms of the same m. p. (Found : C, 46·1; H, 5·9; N, 23·8, 23·65. $C_{11}H_{16}N_5Cl,HCl$ requires C, 45·6; H, 5·9; N,

24·15%). The corresponding *base* crystallised from light petroleum (b. p. 60—80°) as small prisms, m. p. 114—116° (Found: C, 52·15; H, 5·85, N, 27·4. $C_{11}H_{16}N_5Cl$ requires C, 52·1; H, 6·35; N, 27·7%). The *picrate* crystallised from 50% aqueous ethanol as yellow rods, m. p. 150—151° (Found: C, 42·45; H, 4·25; N, 22·85. $C_{11}H_{16}N_5Cl,C_6H_3O_7N_3$ requires C, 42·3; H, 3·95; N, 23·2%).

N^1-p-*Chlorophenyl*-N^2-*methyldiguanide* (IV; X = Cl, R = H, R′ = Me).—*N*-*p*-Chlorophenyl-*N*′-guanylthiourea (Ashworth, Crowther, Curd, Hendry, Richardson, and Rose, *J.*, 1949, 475) (22·85 g.), mercuric oxide (64·8 g.), and aqueous methylamine (66 c.c.; 23% solution) were stirred vigorously in ethanol (900 c.c.) for 16 hr. at room temperature and then for 30 min. on the steam-bath. The filtered solution was evaporated under reduced pressure, to leave a thick oil which set to a glass. This was dissolved in ethyl acetate (500 c.c.), and the solution clarified with kieselguhr. Ethanolic hydrogen chloride precipitated the crude hydrochloride, which was collected, stirred with water (60 c.c.), and filtered. The filtrate was made alkaline by addition of aqueous sodium hydroxide and the precipitated N^1-p-*chlorophenyl*-N^2-*methyldiguanide*, after several recrystallisations from benzene, formed prisms, m. p. 169—170° (Found: C, 48·6; H, 5·4; N, 30·9. $C_9H_{12}N_5Cl$ requires C, 48·0; H, 5·35; N, 31·1%).

4-*Amino*-1-p-*chlorophenyl*-1 : 2-*dihydro*-2 : 2-*dimethyl*-6-*methylamino*-1 : 3 : 5-*triazine* (IX; X = Cl, R = MeNH, R′ = H).—When N^1-*p*-chlorophenyl-N^2-methyldiguanide (4·5 g.), 3·5% hydrochloric acid (40 c.c.), water (10 c.c.), and acetone (25 c.c.) were kept at 50° for 18 hr. and the mixture was worked up in the usual manner, a base was obtained (2·1 g.), melting at 154—155°, then resolidifying and melting with decomposition at 217—219°. This was dissolved in dilute hydrochloric acid and salted out at pH 5 as the monohydrate of 4-*amino*-1-p-*chlorophenyl*-1 : 2-*dihydro*-2 : 2-*dimethyl*-6-*methylamino*-1 : 3 : 5-*triazine hydrochloride*, small prisms, m. p. 228—230° (decomp.), shrinking at 185° (Found: C, 44·75; H, 5·8; N, 22·7. $C_{12}H_{16}N_5Cl,HCl,H_2O$ requires C, 44·9; H, 6·0; N, 22·9%). Ultra-violet absorption in 0·01N-HCl: $\lambda_{max.}$ 236 mμ (ε 15,800) (see Fig. 2). In one experiment in which dilute sulphuric acid was used instead of hydrochloric acid, an improved yield of the base was obtained. The *picrate* crystallised from ethanol as yellow prisms, m. p. 179—181° (Found: C, 43·85; H, 3·85; N, 22·3. $C_{12}H_{16}N_5Cl,C_6H_3O_7N_3$ requires C, 43·8, H, 3·9; N, 22·7%).

4-*Amino*-6-p-*chloroanilino*-1 : 2-*dihydro*-1 : 2 : 2-*trimethyl*-1 : 3 : 5-*triazine* (V; X = Cl, R = H, R′ = Me, R″ = NH_2).—N^1-*p*-Chlorophenyl-N^2-methyldiguanide (5·65 g.), acetone (25 c.c.), and piperidine (0·4 c.c.) were heated together under reflux for 68 hr. The mixture was cooled and the solid obtained (5·1 g.) was collected, and recrystallised from 50% aqueous methanol to give 4-*amino*-6-p-*chloroanilino*-1 : 2-*dihydro*-1 : 2 : 2-*trimethyl*-1 : 3 : 5-*triazine*, prisms, m. p. 223—224° (decomp.) (Found: C, 54·15; H, 5·8; N, 25·95. $C_{12}H_{16}N_5Cl$ requires C, 54·3; H, 6·1; N, 26·4). Ultra-violet absorption: in 0·01N-HCl, $\lambda_{max.}$ 252 mμ (ε 16,600); in 0·1N-NaOH, $\lambda_{max.}$ 249 mμ (ε 15,100). The *picrate* crystallised from ethanol as blunt yellow needles, m. p. 192—195° (Found: C, 44·1; H, 4·05; N, 22·2. $C_{12}H_{16}N_5Cl,C_6H_3O_7N_3$ requires C, 43·8; H, 3·9; N, 22·7%).

When each of the two dihydrotriazines derived from N^1-*p*-chlorophenyl-N^2-methyldiguanide was heated at 100° for 20 min. in 0·1N-sodium hydroxide, the ultra-violet absorption of the solutions ($\lambda_{max.}$ 247 mμ; ε, 13,000) (see Fig. 2) corresponded in each case with that of a mixture of the two isomers containing about 75% of 4-amino-6-*p*-chloroanilino-1 : 2-dihydro-1 : 2 : 2-trimethyl-1 : 3 : 5-triazine.

Isomerization of 4-*Amino*-6-p-*chloroanilino*-1 : 2-*dihydro*-1 : 2 : 2-*trimethyl*-1 : 3 : 5-*triazine* (V; X = Cl, R = H, R′ = Me, R″ = NH_2) *to Form an Equilibrium Mixture.*—The anilino-dihydrotriazine (0·2 g.) in 0·1N-sodium hydroxide (65 c.c.) was heated for 20 min. in a bath at 100°. The cooled solution was made faintly acid (pH 6) with hydrochloric acid and extracted with *n*-butanol (4 × 65 c.c.). The extracts were concentrated under reduced pressure to about 15 c.c. and the volume was made up to 25 c.c. with butanol and enough water to saturate the butanol solution. This was submitted to counter-current distribution in an all-glass machine of the Craig type, employing 48 transfers between 25 c.c. quantities of *n*-butanol (the traversing solvent) and of 0·01N-hydrochloric acid which had previously been equilibrated with each other. The ultra-violet absorption at 236 and 252 mμ (the wave-lengths corresponding with peak absorption for the two isomers in 0·01N-hydrochloric acid) was determined in the aqueous phase from a number of tubes sufficient to give the pattern of the distribution. The concentrations of the two isomers were calculated by the solution of simultaneous equations derived from these values and from the absorption of the pure isomers. Tube 34 provided a solution whose absorption was identical with that of the starting material, and which, on treatment with hot alkali, again gave an equilibrium mixture. Absorption curves typical of the isomeric methylamino-dihydrotriazine (IX;

X = Cl, R = MeNH, R′ = H) were obtained from tubes 20 and 21. The solution in the latter tube was basified and heated for 20 min. at 100° to give again an equilibrium mixture.

N^1N^2-*Di*-p-*chlorophenyldiguanide* (IV; X = Cl, R = H, R′ = *p*-C_6H_4Cl).—Guanidine nitrate (19·6 g.) was added to ethanol (200 c.c.) in which sodium (3·7 g.) had been dissolved and the whole was boiled for 30 min. and filtered. More ethanol (300 c.c.) was added to the filtrate, together with *NN′*-di-*p*-chlorophenylthiourea (23·6 g.) and mercuric oxide (52 g.). After being stirred vigorously at room temperature for 18 hr. and then on the steam-bath for 15 min., the suspension was filtered, and the filtrate was concentrated under reduced pressure (to about 100 c.c.) and mixed with hydrochloric acid (600 c.c.; 2%) which precipitated a mixture of hydrochloride and base. The product was triturated with concentrated hydrochloric acid, collected, dried, dissolved in methanol, and reprecipitated by addition of ethyl acetate, to give N^1N^2-*di*-p-*chlorophenyldiguanide hydrochloride*, rods, m. p. 239—240° (decomp.) (Found: C, 47·0; H, 3·5; N, 20·25. $C_{14}H_{13}N_5Cl_2$,HCl requires C, 46·8; H, 3·95; N, 19·55%).

4-*Amino*-6-p-*chloroanilino*-1-p-*chlorophenyl*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine* (IX; X = Cl, R = *p*-NH·C_6H_4Cl, R′ = H).—(*a*) A mixture of N^1N^2-di-*p*-chlorophenyldiguanide hydrochloride (10·8 g.), acetone (55 c.c.), water (45 c.c.), and N-hydrochloric acid (30 c.c.) was stirred and heated under reflux on the steam-bath for 20 hr. Acetone was distilled off under reduced pressure and the residual suspension was mixed with ether and treated, in the cold, with an excess of aqueous sodium hydroxide. The undissolved solid was still mainly hydrochloride which was recrystallised from 40% aqueous ethanol and then dissolved in ethanol and reprecipitated by addition of dilute hydrochloric acid, to give the sesquihydrate of 4-*amino*-6-p-*chloroanilino*-1-p-*chlorophenyl*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine hydrochloride*, decomp. 134° (Found: C, 47·9; H, 5·2; N, 16·1; loss in wt. in a vacuum at 110°, 5·8. $C_{17}H_{17}N_5Cl_2$,HCl,1·5H_2O requires C, 47·9; H, 4·95; N, 16·5; H_2O, 6·3%). Ultra-violet absorption: in 0·01N-HCl, $\lambda_{max.}$ 248 mμ (ε 19,600); in 0·1N-NaOH, $\lambda_{max.}$ 244 mμ (ε 17,200). The absorption was unchanged after treatment with 0·1N-sodium hydroxide at 100° for 20 min. The *base* crystallised from 40% aqueous ethanol as irregular prisms, m. p. 196—197° (Found: C, 55·55; H, 4·9; N, 19·55. $C_{17}H_{17}N_5Cl_2$ requires C, 56·3; H, 4·75; N, 19·35%). The *picrate* formed yellow rods (from ethanol), m. p. 247—249° (Found: C, 47·1; H, 3·3; N, 18·8. $C_{17}H_{17}N_5Cl_2$,$C_6H_3O_7N_3$ requires C, 46·7; H, 3·4; N, 18·95%).

(*b*) A mixture of N^1N^2-di-*p*-chlorophenyldiguanide (from the hydrochloride and ethanolic sodium ethoxide) (3·2 g.), acetone (12 c.c.), and piperidine (0·2 c.c.) was heated under reflux for 66 hr. The hot solution was treated with carbon and filtered. The filtrate was diluted with water (30 c.c.) to precipitate a crude base (2·25 g.). This was converted into a hydrochloride and a picrate, each of which was identical (m. p. and mixed m. p.) with the corresponding derivative obtained by method (*a*) above.

4-*Amino*-6-*anilino*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1-*phenyl*-1 : 3 : 5-*triazine* (IX; X = H, R = NHPh, R′ = H).—N^1N^2-Diphenyldiguanide (Cramer, *Ber.*, 1901, **34**, 2597) (3·15 g.), N-hydrochloric acid (25 c.c.), acetone (15 c.c.), and water (5 c.c.) were heated together for 20 hr. on the steam-bath. Concentration of the solution under reduced pressure, followed by basification and ether-extraction under ice-cold conditions, left an insoluble base (1·35 g.), m. p. 171—174°. It was dissolved in 10% hydrochloric acid, and aqueous ammonia was added to give a pH of 5. The solid thus precipitated was collected, dissolved in water, and salted out with saturated aqueous sodium chloride, to give very small colourless rods of the dihydrate of 4-*amino*-6-*anilino*-1 : 2-*dihydro*-2 : 2-*dimethyl*-1-*phenyl*-1 : 3 : 5-*triazine hydrochloride*, m. p. 236—237° (Found: C, 55·25; H, 6·35; N, 18·9. $C_{17}H_{19}N_5$,HCl,2H_2O requires C, 55·75; H, 6·6; N, 19·15%). Ultra-violet absorption: in 0·01N-HCl, $\lambda_{max.}$ 248 mμ (ε 20,500); in 0·1N-NaOH, $\lambda_{max.}$ 246 mμ (ε 12,800). The yellow *picrate*, crystallised from 2-ethoxyethanol, had m. p. 236—238° (decomp.) (Found: C, 52·65; H, 4·45; N, 21·4. $C_{17}H_{19}N_5$,$C_6H_3O_7N_3$ requires C, 52·9; H, 4·25; N, 21·5%).

4 : 6-*Diamino*-1 : 2-*dihydro*-1 : 2-*diphenyl*-1 : 3 : 5-*triazine*.—Aniline hydrochloride (25·9 g.) and dicyandiamide (21 g.) were stirred together in water (50 c.c.) on the steam-bath for 1 hr. A solution of benzaldehyde (42·4 g.) in ethanol (100 c.c.), and hydrochloric acid (17·5 c.c.; *d* 1·18) were added and the mixture was stirred at 70° for 17 hr. Carbon was then added and the mixture was filtered, and evaporated almost to dryness under reduced pressure. Water (200 c.c.) was added and the solution was evaporated under reduced pressure to half its volume. The solid which separated on keeping at 0° for some time was collected, washed with water, then dissolved in water, cooled to 0°, and shaken with ether whilst sodium hydroxide solution was added. The precipitated base was collected, washed with ether, and dried. It was dissolved in dilute hydrochloric acid, and the solution was clarified, and neutralised with aqueous ammonia

to precipitate the colourless *hydrochloride*, m. p. 232—233° (from water) (Found: C, 59·65; H, 5·4; N, 23·2. $C_{15}H_{15}N_5$,HCl requires C, 59·75; H, 5·3; N, 23·2%). Ultra-violet absorption in 0·01N-HCl: $\lambda_{max.}$ 249 mμ (ε 8,600).

Reaction of Benzylideneaniline with Dicyandiamide.—(*a*) Benzylideneaniline (10 g.) was added to a solution of dicyandiamide (4·65 g.) in water (125 c.c.) and 7% hydrochloric acid (27·7 c.c.). The mixture was stirred at 70° for 24 hr. and cooled and the oil present was discarded. Carbon was added and the mixture was filtered. The filtrate was cooled to 0° and made strongly alkaline with sodium hydroxide solution. The precipitate was collected, washed with ether, and dried. The base was dissolved in dilute hydrochloric acid, and the solution was clarified, and neutralised with aqueous ammonia. The solid was collected, washed with water, and crystallised from water, to give 4 : 6-diamino-1 : 2-dihydro-1 : 2-diphenyl-1 : 3 : 5-triazine hydrochloride, m. p. 221—224° undepressed by the product of the preceding experiment (Found: C, 59·45; H, 5·55; N, 23·45%). Ultra-violet absorption in 0·01N-HCl: $\lambda_{max.}$ 249 mμ (ε 9300).

(*b*) The initial mixture as in (*a*) was neutralised by the addition of aqueous ammonia and then stirred at 70° for 18 hr. The benzylideneaniline was unchanged.

IMPERIAL CHEMICAL INDUSTRIES LIMITED, DYESTUFFS DIVISION,
HEXAGON HOUSE, BLACKLEY, MANCHESTER, 9. [*Received, October 28th*, 1953.]

The Halides of Niobium (Columbium) and Tantalum. Part IV. The Electrical Conductivities of Niobium and Tantalum Pentafluorides.*

By FRED FAIRBROTHER, WILLIAM C. FRITH, and ALFRED A. WOOLF.

[Reprint Order No. 4756.]

The conductivites of liquid niobium and tantalum pentafluorides have been measured over a range of temperatures. The specific conductivities at the melting points are respectively, NbF_5, $1·63 \times 10^{-5}$ ohm^{-1} cm.$^{-1}$ at 80·0°; TaF_5, 1·56 ohm^{-1} cm.$^{-1}$ at 95·1°, and the activation energies of the molar conductivites 8·1 and 6·7 kcal. mole^{-1}. The results indicate a partial ionisation of these compounds, probably into MF_6^- and MF_4^+.

IN Part III of this series * it was noted that niobium and tantalum pentafluorides possessed marked catalytic properties in a number of Friedel–Crafts type reactions, and entropies of vaporisation of the liquids (Trouton constants) higher than normal. These results suggested some degree of association of the molecules in the liquid state and possibly a partial self-ionisation of the form $(NbF_5)_2 \rightleftharpoons NbF_6^- + NbF_4^+$. The latter point has now been examined by the measurement of the electrical conductivities of the fused pentafluorides. The temperature coefficients of these conductivities are positive. The activation energies of the specific conductivities, calculated from the slope of the $\log_{10}\kappa$–$1/T$ curve, are 7·52 kcal. mole^{-1} for NbF_5 and 6·42 kcal. mole^{-1} for TaF_5. The corresponding activation energies for the molar conductivities ($\kappa M/d$) involve a knowledge of the densities of the molten fluorides. If we assume that the densities of molten NbF_5 are as given by Junkins *et al.* (*J. Amer. Chem. Soc.*, 1952, **74**, 3464) and that the densities of TaF_5 (for which no experimental data are available) are 1·44 times greater, which is the ratio of the densities of the solids (Ruff and Schiller, *Z. anorg. Chem.*, 1911, **72**, 329) and also roughly that of their molecular weights, the activation energies of the molar conductivities are 8·1 kcal. mole^{-1} for NbF_5 and 6·7 kcal. mole^{-1} for TaF_5. It may also be noted, in connection with this assumption regarding the densities of TaF_5, that the molecular dimensions in the gas phase of the pentachlorides and of the pentabromides are almost identical (Skinner and Sutton, *Trans. Faraday Soc.*, 1940, **36**, 668).

It is known (Bloom and Heymann, *Proc. Roy. Soc.*, 1946, *A*, **158**, 392) that in many cases the variation with temperature of the specific conductivity (κ) of molten salts of a predominantly ionic character can be represented by a simple exponential equation, $\kappa = \kappa_0 e^{-E_\kappa/RT}$ where E_κ is the activation energy of ionic migration, deviations from this equation being sometimes found for partially covalent compounds, *e.g.*, $ZnCl_2$, $PbCl_2$. It

* Part III, *J.*, 1951, 3051.

may be observed that in the case of niobium and tantalum pentafluorides, although these are predominantly covalent, the exponential relation holds over the entire range of measurement.

Bloom and Heymann (*loc. cit.*) also note that the energy of ionic migration (E_κ) is always smaller than the activation energy of viscous flow. The relationship between these two magnitudes has been discussed at length by Greenwood and Martin (*J.*, 1953, 1427) who have shown that, for a large number of molten picrates and boron trifluoride co-ordination compounds, the ratio of the activation energies of viscous flow (E_η) and of ionic migration (E_μ)—the latter being calculated from the *molar* conductivities—is very close to unity. In the case of some high-melting inorganic solids, *e.g.*, the alkali-metal halides and silver halides, where there is a considerable disparity between the radii of anion and cation, and where different structural processes may be involved in viscous flow and in ionic migration, the ratio E_η/E_μ may be greater than unity, with an average value of 4·0. The present work suggests that in the case of niobium and tantalum pentafluorides the ratio E_η/E_μ is *less* than unity.

No experimental data are available for the viscosities of these fluorides (though visual comparison with other liquids suggests that they are of the order of 20 centipoises), but an estimate of the activation energies of viscous flow may be obtained from thermodynamic data. Kincaid, Eyring, and Stern (*Chem. Reviews*, 1941, **28**, 301) have put forward evidence to show that the activation energy of viscous flow is related to the energy of vaporisation and cite a large number of experimental figures to show that in general it lies between one-third and one-quarter of this magnitude. The latent heats of vaporisation as determined by Fairbrother and Frith (Part III) being used, the activation energy of viscous flow for both compounds should lie between 3 and 4 kcal. On this basis, therefore, the ratio E_η/E_μ for niobium pentafluoride and tantalum pentafluoride, is at the most about 0·5 and 0·6 respectively. Such data as are available (Woolf and Greenwood, *J.*, 1950, 2200) indicate that in the case of antimony pentafluoride and arsenic trifluoride also, the value of this ratio is less than unity.

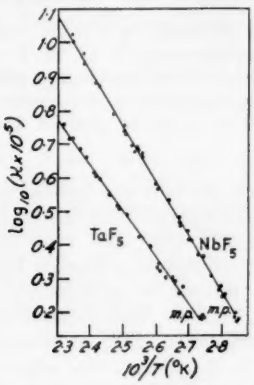
The ionisation of niobium and tantalum pentafluorides has been formally represented as that of a definite dimeric species, *viz.*, $(NbF_5)_2 \rightleftharpoons NbF_6^- + NbF_4^+$. The nature of the association in the molten fluorides may, however, be less that of a simple dimerisation than of a more generalised interaction between one fluoride molecule and its neighbours resulting from the strong electron-acceptor character of the molecules—as indicated by their Friedel–Crafts activity—and the negative character of the fluorine atoms. It does, however, seem probable that the ions involved in the conduction process are the hexafluoro- and tetrafluoro- anion and cation respectively.

Experimental

The pentafluorides were prepared and purified as already described (Part III, *loc. cit.*) by the action of gaseous fluorine on the pure metals, followed by repeated fractional sublimation in a vacuum and transfer to small hook-ended ampoules. The same trouble was experienced, as previously noted, of the cracking of the glass apparatus on attempting to remelt a specimen of niobium pentafluoride which had been allowed to melt and solidify, a consequence of the polymorphic expansion which takes place below the melting point.

The conductivity cell was constructed of Pyrex glass, the platinum electrodes being silver-soldered to stout tungsten leads. The carefully purified fluoride, contained in a sealed ampoule, was sealed *in vacuo* in a side arm of the cell, which had been previously thoroughly out-gassed. The ampoule was broken, and the fluoride melted and allowed to cover the electrodes. At no stage after the initial transfer into the purification line were the fluorides allowed to come into contact with the atmosphere. The conductivity measurements were carried out in the sealed cell immersed in an oil-thermostat which could be maintained at any desired temperature to ±0·2°. Measurements were made, with 1000-cycle A.C., during 3 days (the fluoride not being allowed to solidify) at a series of temperatures from near the m. p.s to about 160°. Higher temperatures were not used, since experiments had shown that these fluorides attack Pyrex glass with a rapidity which increases very quickly with rise of temperature and is very marked above about 160°. In the present work the negligible amount of attack on the glass was shown

by the smallness of the variation of the conductivity over 72 hr. The cell constant changed by little more than 1% over the entire series of measurements: in the calculation of specific conductivity, the mean cell constant (0·277) was used. Both liquid fluorides could be supercooled considerably, so that specific conductivites at the m. p.s could be obtained by interpol-



ation. These (in ohm^{-1} cm.$^{-1}$) were $1{\cdot}65 \times 10^{-5}$ and $1{\cdot}56 \times 10^{-5}$ for NbF_5 at 80° and for TaF_5 at 95·1°, respectively. The specific conductivities are tabulated below and the plots of $\log_{10} \kappa$ against $1/T$ are given in the Figure.

Niobium pentafluoride.

t	$10^5\kappa$	Time, hr.	t	$10^5\kappa$	Time, hr.	t	$10^5\kappa$	Time, hr.	t	$10^5\kappa$	Time, hr.
78·9°	1·54	0·5	102·0°	2·90	—	126·5°	5·37	—	119·1°	4·70	—
79·1	1·51	—	101·8	2·88	—	132·2	6·16	—	118·8	4·60	—
79·0	1·51	—	111·4	3·68	—	141·1	7·60	—	112·2	3·80	—
79·2	1·52	—	121·6	4·76	—	147·1	8·73	—	106·8	3·40	—
78·8	1·51	—	123·0	4·96	—	153·4	10·15	35·0	107·2	3·41	—
84·3	1·76	—	79·4	1·55	—	126·5	5·49	50·0	102·2	3·01	59·0
84·2	1·78	—	79·5	1·56	20·0	154·1	10·55	—	98·7	2·74	—
88·7	2·01	—	120·4	4·90	—	148·0	9·29	—	92·5	2·31	—
93·8	2·33	4·0	120·1	4·82	—	139·4	7·54	—	85·1	1·88	—
97·6	2·57	—	119·9	4·80	24·0	127·1	5·66	—	85·6	1·89	72·0
97·4	2·57	—									

Tantalum pentafluoride.

t	$10^5\kappa$	Time, hr.	t	$10^5\kappa$	Time, hr.	t	$10^5\kappa$	Time, hr.	t	$10^5\kappa$	Time, hr.
111·0°	2·15	4·5	119·7°	2·64	—	149·3°	4·88	—	104·3°	2·00	39·5
110·2	2·11	—	129·8	3·26	—	154·1	5·23	24·0	103·8	1·97	—
107·7	2·01	—	129·6	3·24	—	152·9	5·22	—	100·3	1·83	—
101·6	1·81	—	141·2	4·08	—	153·1	5·25	—	92·3	1·52	—
101·8	1·81	—	140·7	4·04	—	145·6	4·59	—	92·3	1·52	—
110·8	2·20	—	139·1	3·99	—	134·0	3·57	—	92·5	1·51	—
110·9	2·21	—	158·0	5·75	—	125·7	3·10	—	92·6	1·53	72·0
119·7	2·64	—	149·3	4·88	—	114·7	2·48	—	92·9	1·52	—

Attempts were also made to determine the decomposition potentials of the two pentafluorides. This, however, was found to be impracticable on account of a considerable polarisation at the electrodes. Application of a constant potential to the electrodes gave a current which decreased with time, and on reversal of the potential, the back E.M.F. then manifested itself by a current which was greater than that corresponding to the potential and the A.C. resistance of the cell.

We are indebted to Imperial Chemical Industries Limited, General Chemicals Division, for the provision of the fluorine cell.

THE UNIVERSITY OF MANCHESTER. [*Received, October 28th,* 1953.]

Halogenated o- *and* p-*Phenolic Ketones.*

By Ng. Ph. Buu-Hoï, Ng. D. Xuong, and Denise Lavit.

[Reprint Order No. 4817.]

Synthesis, by various methods, of a wide series of *o*- and *p*-phenolic ketones bearing halogen substituents (F, Cl, Br, I) is reported; bromination of 4-hydroxyacetophenone and its homologues takes place in the benzene nucleus or in the side chain, according to the experimental conditions. These halogenated ketones and a series of derived indoles were prepared for biological testing.

Phenolic ketones bearing halogen atoms in the nucleus are of manifold biological interest. Chloro- and bromo-diaryl ketones frequently display high tuberculostatic activity *in vitro* (cf. Buu-Hoï, *Compt. rend.*, 1945, **221**, 202; *Rec. Trav. chim.*, 1949, **68**, 769; Kuhn *et al.*, *Ber.*, 1952, **85**, 72); 4-hydroxyacetophenones bearing halogen substituents in the 3- and the 5-position are structurally related to antagonists of thyroxine (cf. Lerman and Harington, *J. Clin. Invest.*, 1948, **27**, 546; Wilkinson, Sheehan, and Maclagan, *Biochem. J.*, 1951, **48**, 188; **49**, 710); a substance such as 4-hydroxy-3 : 5-di-iodohexanophenone would be very similar in shape to the biologically active *n*-butyl 4-hydroxy-3 : 5-di-iodobenzoate (Barker, Dirks, Garlick, and Klitgaard, *Proc. Soc. Exper. Biol. Med.*, 1951, **78**, 840), recently described as a pituitary inhibitor. A broad investigation was therefore undertaken of the synthesis of hydroxy-ketones containing one or more atoms of fluorine, chlorine, bromine, or iodine.

o-Fluoroanisole readily underwent Friedel–Crafts acylation with both aliphatic and aromatic acid chlorides, to give a series of 4-acyl-2-fluoroanisoles, which were converted into the corresponding 4-acyl-2-fluorophenols by means of pyridine hydrochloride. Bromination of these phenols in aqueous acetic acid gave 4-acyl-2-bromo-6-fluorophenols. The fluorinated ketones, listed in Table 1, bear structural resemblance to compounds such

Table 1. *Fluoro-ketones.*

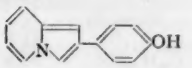
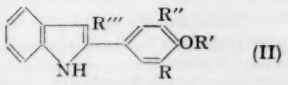
Ketone	M. p	Formula	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
3-Fluoro-4-methoxyvalerophenone [a]	liquid	$C_{12}H_{15}O_2F$	68·5	7·2	68·6	7·1
3-Fluoro-4-hydroxyvalerophenone	49°	$C_{11}H_{13}O_2F$	67·0	6·4	67·3	6·6
3-Fluoro-4-methoxyhexanophenone	62	$C_{13}H_{17}O_2F$	69·4	7·5	69·6	7·6
3-Fluoro-4-hydroxyhexanophenone [b]	64	$C_{12}H_{15}O_2F$	68·6	7·3	68·6	7·1
1-Decanoyl-3-fluoro-4-methoxybenzene [c]	72	$C_{17}H_{25}O_2F$	73·1	8·8	72·9	8·9
1-Decanoyl-3-fluoro-4-hydroxybenzene [d]	67	$C_{16}H_{23}O_2F$	72·0	8·6	72·2	8·6
3-Fluoro-4-methoxybenzophenone	97	$C_{14}H_{11}O_2F$	73·1	4·8	73·0	4·8
3-Fluoro-4-hydroxybenzophenone	123	$C_{13}H_9O_2F$	72·0	4·3	72·2	4·2
3-Fluoro-4-methoxy-1-phenacetylbenzene	113	$C_{15}H_{13}O_2F$	73·7	5·2	73·8	5·3
3-Fluoro-4-hydroxy-1-phenacetylbenzene	140	$C_{14}H_{11}O_2F$	73·1	4·8	73·0	4·8
3-Bromo-5-fluoro-4-hydroxyacetophenone	173	$C_8H_6O_2BrF$	41·4	2·9	41·2	2·6
3-Bromo-5-fluoro-4-hydroxypropiophenone	114	$C_9H_8O_2BrF$	43·9	3·5	43·7	3·2
3-Bromo-5-fluoro-4-hydroxybutyrophenone	97	$C_{10}H_{10}O_2BrF$	45·7	3·9	46·0	3·8
3-Bromo-5-fluoro-4-hydroxyvalerophenone	87	$C_{11}H_{12}O_2BrF$	47·8	4·7	48·0	4·4
3-Bromo-5-fluoro-4-hydroxyhexanophenone	95	$C_{12}H_{14}O_2BrF$	49·5	4·8	49·8	4·8
1-Decanoyl-3-bromo-5-fluoro-4-hydroxybenzene	68	$C_{16}H_{22}O_2BrF$	55·6	6·5	55·6	6·4
3-Bromo-5-fluoro-4-hydroxybenzophenone	187	$C_{13}H_8O_2BrF$	53·1	2·9	52·9	2·7
3-Bromo-5-fluoro-4-hydroxy-1-phenacetylbenzene	165	$C_{14}H_{10}O_2BrF$	54·4	3·5	54·4	3·2

[a] B. p. 198—201°/32 mm., n_D^{28} 1·5350. [b] B. p. 200°/15 mm. [c] B. p. 232—233°/20 mm. [d] B. p. 233—234°/20 mm.

as 3-fluoro-4-hydroxypropiophenone (Buu-Hoï, Xuong, and Lavit, *J. Org. Chem.*, 1953, **18**, 910), 3-fluorotyrosine (Schiemann, "Die organischen Fluorverbindungen," 1950, Steinkopf, Frankfurt a.M.), and 3-fluoro-4-hydroxyphenylacetic acid, which are active in Graves–Basedow's disease (May, "Die Basedowsche Krankheit, Jod und Fluor," 1950, Editio Cantor, Aulendorf i.W.). The same sequence of reactions was used for preparing 3-bromo-5-chloro-4-hydroxypropiophenone *via* 3-chloro-4-hydroxypropiophenone.

An interesting observation was made during the study of bromination of 4-acylphenols.

4-Hydroxyacetophenone reacting with one molecule of bromine in acetic acid gave ω-bromo-4-hydroxyacetophenone, whose constitution was determined by the formation of 2-*p*-hydroxyphenylpyrrocoline (I) in the reaction with 2-picoline (cf. Tschitschibabin, *Ber.*, 1927, **60**, 1607); 4-hydroxypropiophenone similarly gave α-bromo-4-hydroxypropiophenone, in whose molecule the halogen atom was proved to be on the side chain by removal with aniline; under the same conditions, 3-bromo-4-hydroxypropiophenone

(I)  (II) 

(Hoán and Buu-Hoï, *Compt. rend.*, 1947, **224**, 1363) was unchanged. In aqueous acetic acid 3 : 5-dibromo-4-hydroxyacetophenone (Priestley and Moness, *J. Org. Chem.*, 1940, **5**, 358) and 3 : 5-dibromo-4-hydroxypropiophenone were obtained; a compound prepared by Goldzweig and Kaiser (*J. pr. Chem.*, 1891, **43**, 86) from 4-hydroxypropiophenone and aqueous bromine was found to consist mainly of the latter compound. Further nuclear bromo-ketones synthesised in the course of this work are listed in Table 2; ketones containing bromine in the side chain were not intermediates in the nuclear halogenation, as no rearrangement took place in acidic or in basic media.

TABLE 2. *Bromo- and Chloro-ketones.*

Ketone [a]	M. p.	Formula	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
3 : 5-Dibromo-4-methoxybutyrophenone	53°	$C_{11}H_{12}O_2Br_2$	39·2	3·8	39·3	3·6
3 : 5-Dibromo-4-hydroxybutyrophenone	117	$C_{10}H_{10}O_2Br_2$	37·5	3·0	37·3	3·1
3 : 5-Dibromo-4-hydroxyvalerophenone	75	$C_{11}H_{12}O_2Br_2$	39·1	3·5	39·3	3·6
3 : 5-Dibromo-4-hydroxyhexanophenone	68	$C_{12}H_{14}O_2Br_2$	40·8	4·2	41·1	4·0
3 : 5-Dibromo-4-hydroxyheptanophenone	71	$C_{13}H_{16}O_2Br_2$	43·0	4·2	42·9	4·4
1-Decanoyl-3 : 5-dibromo-4-hydroxybenzene	54	$C_{16}H_{22}O_2Br_2$	47·4	5·2	47·3	5·4
3 : 5-Dibromo-4-hydroxy-1-phenacetylbenzene [b]	144	$C_{14}H_{10}O_2Br_2$	45·1	2·8	45·4	2·7
3-Bromo-5-chloro-4-methoxypropiophenone	57	$C_{10}H_{10}O_2BrCl$	43·0	3·8	43·2	3·6
3-Bromo-5-chloro-4-hydroxypropiophenone	125	$C_9H_8O_2BrCl$	40·7	3·0	41·0	3·0
2-Bromo-4-2′-thenoyl)anisole	127	$C_{12}H_9O_2BrS$	48·2	3·2	48·5	3·0
2-Bromo-4-2′-thenoyl)phenol	183	$C_{11}H_7O_2BrS$	46·4	2·6	46·6	2·5
2-Bromo-4-(5-methyl-2-thenoyl)anisole	142	$C_{13}H_{11}O_2BrS$	50·0	3·4	50·2	3·5
2-Bromo-4-(5-methyl-2-thenoyl)phenol	188	$C_{12}H_9O_2BrS$	48·1	3·1	48·5	3·0
2-Chloro-4-2′-thenoylanisole [c]	124	$C_{12}H_9O_2ClS$	56·9	3·5	57·0	3·6
2-Chloro-4-2′-thenoylphenol	180	$C_{11}H_7O_2ClS$	55·0	3·0	55·3	2·9
2-Chloro-4-(5-methyl-2-thenoyl)anisole [d]	143	$C_{13}H_{11}O_2ClS$	58·2	4·0	58·5	4·1
2-Chloro-4-(5-methyl-2-thenoyl)phenol	183	$C_{12}H_9O_2ClS$	56·8	3·8	57·0	3·6
3 : 4′-Dichloro-4-methoxybenzophenone [e]	125	$C_{14}H_{10}O_2Cl_2$	59·4	3·4	59·7	3·6
3 : 4′-Dichloro-4-hydroxybenzophenone	168	$C_{13}H_8O_2Cl_2$	58·2	3·2	58·4	3·0
2′ : 3-Dichloro-4-methoxybenzophenone [f]	131	$C_{14}H_{10}O_2Cl_2$	59·4	3·6	59·7	3·6
2′ : 3-Dichloro-4-hydroxybenzophenone	156	$C_{13}H_8O_2Cl_2$	58·3	3·3	58·4	3·0
4-Chloro-2-2′-furoylanisole [g]	—	$C_{12}H_9O_3Cl$	60·6	3·8	60·9	3·8
4-Chloro-2-2′-furoylphenol	96	$C_{11}H_7O_3Cl$	59·2	3·1	59·3	3·1
3 : 4′-Dichloro-6-methoxybenzophenone	131	$C_{14}H_{10}O_2Cl_2$	59·5	3·5	59·7	3·6
2′ : 3-Dichloro-6-methoxybenzophenone	108	$C_{14}H_{10}O_2Cl_2$	59·5	3·8	59·7	3·6
2′ : 5-Dichloro-2-hydroxy-4-methylbenzophenone	105	$C_{14}H_{10}O_2Cl_2$	59·6	3·4	59·7	3·6

[a] In the case of Friedel–Crafts reactions involving 2-furoyl, 2-thenoyl, and 5-methyl-2-thenoyl chloride, the contact with aluminium chloride was reduced to 2—4 hours. The ketones derived from aliphatic acid chlorides were recrystallised from benzene–ligroin; those derived from aromatic and heterocyclic acid chlorides were recrystallised from methanol or ethanol. [b] An *x* : *x*′-dibromo-4-hydroxydeoxybenzoin, m. p. 138—142°, prepared by Glassner (*Monatsh.*, 1907, **28**, 291) by bromination of 4-hydroxydeoxybenzoin-3-carboxylic acid, was probably an impure sample of the present compound. [c] B. p. 240°/13 mm. [d] B. p. 250°/13 mm. [e] B. p. 252°/13 mm. [f] B. p. 243°/13 mm. [g] B. p. 220°/13 mm.

Halogenation of 4-hydroxypropiophenone with iodine and yellow mercuric oxide in ethanol yielded 4-hydroxy-3 : 5-di-iodopropiophenone, which was kindly tested by Mrs. Pitt-Rivers (at the National Institute for Medical Research, London) and shown to have no antithyroxine action as assayed by the method of goitre prevention in rats; several higher homologues of this compound were prepared in the same way.

Most of the nuclear-halogenated ketones described in this work retained their halogen

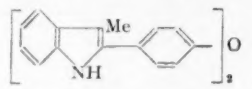
atoms when heated with phenylhydrazine, and Fischer cyclisation of the resulting hydrazones yielded a series of indoles (II) (see Table 3), together with some non-halogenated compounds; bis-indoles could also be prepared in the same way, 4 : 4′-di-propionyldiphenyl oxide giving 4 : 4′-di-(3-methyl-2-indolyl)diphenyl oxide (III).

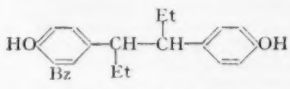
TABLE 3. 2 : 3-*Disubstituted indoles.*

Substituents	M. p.	Formula	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
3-Ethyl-2-*p*-hydroxyphenyl- [a]	122°	$C_{16}H_{15}ON$	81·2	6·4	81·0	6·3
2-*p*-Hydroxyphenyl-3-phenyl-	152	$C_{20}H_{15}ON$	84·0	5·2	84·2	5·3
2-(3-Fluoro-4-hydroxyphenyl)-3-methyl-	90	$C_{15}H_{12}ONF$	75·0	5·3	74·7	5·0
2-(3-Fluoro-4-hydroxyphenyl)-3-phenyl-	139	$C_{20}H_{14}ONF$	79·2	4·5	79·2	4·6
2-(3-Chloro-4-hydroxyphenyl)-3-methyl- [b]	104	$C_{15}H_{12}ONCl$	69·8	4·7	69·9	4·7
2-(3-Bromo-4-hydroxyphenyl)-3-methyl- [c]	109	$C_{15}H_{12}ONBr$	59·9	4·3	59·6	4·0
2-(3-Chloro-4-methoxyphenyl)-3-methyl- [d]	151	$C_{16}H_{14}ONCl$	70·5	5·2	70·7	5·2
2-(3-Bromo-4-methoxyphenyl)-3-methyl-	155	$C_{16}H_{14}ONBr$	60·5	4·6	60·8	4·4
2-(3-Fluoro-4-methoxyphenyl)-3-phenyl-	135	$C_{21}H_{16}ONF$	79·3	5·1	79·5	5·0
2-(3 : 5-Dibromo-4-hydroxyphenyl)-3-methyl-	168	$C_{15}H_{11}ONBr_2$	47·5	2·9	47·2	2·9
2-(3-Bromo-5-chloro-4-hydroxyphenyl)-3-methyl-	151	$C_{15}H_{11}ONBrCl$	53·6	3·3	53·4	3·3
2-(3 : 5-Dibromo-4-hydroxyphenyl)-3-ethyl- [e]	144	$C_{16}H_{13}ONBr_2$	48·5	3·5	48·6	3·3
2-(3 : 5-Dibromo-4-hydroxyphenyl)-	151	$C_{20}H_{13}ONBr_2$	54·3	3·1	54·2	2·9
2-(3-Bromo-5-fluoro-4-hydroxyphenyl)-3-phenyl-	162	$C_{20}H_{13}ONBrF$	63·0	3·2	62·8	3·4
2-(3 : 5-Dibromo-4-hydroxyphenyl)-3-*n*-octyl-	70	$C_{22}H_{25}ONBr_2$	55·3	5·5	55·1	5·2

[a] Deep brown picrate, m. p. 136°. [b] Dark brown picrate, m. p. 148°. [c] Dark brown picrate, m. p. 158°. [d] Brown-violet picrate, m. p. 120°. [e] Brown-violet picrate, m. p. 121°.

The halogenated hydroxybenzophenones and heterocyclic furan and thiophen analogues, obtained by pyridine hydrochloride demethylation of the corresponding methyl ethers (prepared by Friedel–Crafts reaction with halogenated anisoles and homologues), showed notable tuberculostatic activity *in vitro*, which, however, was considerably reduced

(III) 

 (IV)

or suppressed in the presence of blood serum. For similar biological investigation, 3-benzoylhexœstrol (IV) was synthesised by pyridine hydrochloride demethylation of the methyl ether obtained in Friedel–Crafts benzoylation of hexœstrol dimethyl ether; 3-*p*-anisoylhexœstrol dimethyl ether was also prepared.

EXPERIMENTAL (with M. R. KHENISSI).

Preparation of Intermediates.—o-Fluoroanisole was prepared from *o*-anisidine by the Schiemann reaction. *p*-Acylphenols were prepared by refluxing for 30 min. a mixture of the *p*-acylanisole (1 part) and redistilled pyridine hydrochloride (3—4 parts); after addition of water, the product was taken up in chloroform and purified by vacuum-distillation. *p*-Acylanisoles were prepared by Friedel–Crafts reaction with aluminium chloride and the acid chloride in carbon disulphide; as by-products, ethylenic compounds were obtained (cf. Xuong and Buu-Hoï, *J.*, 1952, 3741). 1 : 1-*Di*-p-*anisoylhept*-1-*ene*, from heptanoyl chloride and anisole, formed a pale yellow oil, b. p. 250—252°/15 mm., n_D^{23} 1·5810 (Found: C, 81·1; H, 8·5. $C_{21}H_{26}O_2$ requires C, 81·3; H, 8·4%); 1 : 1-*di*-p-*anisoylhex*-1-*ene*, from hexanoyl chloride and anisole, was also a pale yellow oil, b. p. 242—244°/15 mm., n_D^{22} 1·5950 (Found: C, 81·0; H, 8·2. $C_{20}H_{24}O_2$ requires C, 81·1; H, 8·1%).

3-*Chloro*-4-*hydroxypropiophenone*.—(a) *By demethylation.* A mixture of 3-chloro-4-methoxypropiophenone (50 g.) and redistilled pyridine hydrochloride (200 g.) was refluxed for 15 min.; the *phenol* obtained in 75% yield on dilution with water was purified by vacuum-distillation; it formed shiny colourless prisms, m. p. 114°, from aqueous acetic acid (Found: C, 58·2; H, 5·1. $C_9H_9O_2Cl$ requires C, 58·5; H, 4·9%).

(b) *By chlorination.* 4-Hydroxypropiophenone was best prepared in bulk by saturating a mixture of equal parts of phenol and propionic acid with boron trifluoride at 70—75°; the ketone, obtained in 65—70% yield, was characterised as the *semicarbazone*, needles, m. p. 183° (from ethanol) (Found: N, 20·0. $C_{10}H_{13}O_2N_3$ requires N, 20·3%), oxime, prisms, m. p. 141°

(from aqueous methanol), and 2 : 4-dinitrophenylhydrazone, red needles, m. p. 254—255° (from acetic acid).

4-*Propionyloxypropiophenone* (prepared by use of propionyl chloride) formed colourless prisms, m. p. 68°, from ligroin (Found : C, 69·8; H, 6·7. $C_{12}H_{14}O_3$ requires C, 69·9; H, 6·8%); 4-n-*butyryloxypropiophenone* formed prisms, m. p. 52°, from ligroin (Found : C, 70·7; H, 7·5. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%), and 4-*benzoyloxypropiophenone* formed needles, m. p. 116°, from methanol (Found : C, 75·5; H, 5·8. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·5%).

To a suspension of 4-hydroxypropiophenone (50 g.) in cold acetic acid (800 c.c.), a solution of chlorine (24 g.) in acetic acid (850 c.c.) was added in small portions; the clear solution obtained was kept overnight, concentrated in a vacuum, and diluted with water, giving 35 g. of 3-chloro-4-hydroxypropiophenone.

Action of Bromine on 4-*Hydroxyacetophenone.*—(a) *Side-chain bromination.* To a cooled solution of 4-hydroxyacetophenone (5 g.) in acetic acid (150 c.c.), a solution of bromine (5·9 g.) in acetic acid (30 c.c.) was added in small portions with stirring. The mixture was kept for 1 hr. at room temperature, concentrated in a vacuum, and poured into water; the precipitated oily ω-bromo-4-hydroxyacetophenone gradually solidified, and formed from benzene needles (5 g.), m. p. 130°, highly lachrymatory and irritant (Found : C, 44·4; H, 3·2. $C_8H_7O_2Br$ requires C, 44·6; H, 3·2%).

(b) *Nuclear bromination.* A solution of 4-hydroxyacetophenone (4·5 g.) in aqueous acetic acid (25 c.c. of acid and 65 c.c. of water) was treated with a solution of bromine (10·6 g.) in 80% aqueous acetic acid (25 c.c.) in small portions; on addition of water, 3 : 5-dibromo-4-hydroxyacetophenone (6 g.), m. p. 181°, was obtained (Priestley and Moness, *loc. cit.*); substantial amounts of the same ketone were also obtained when one mol. of bromine was used.

2-p-*Hydroxyphenylpyrrocoline* (I).—A solution of ω-bromo-4-hydroxyacetophenone (1·2 g.) and α-picoline (0·5 g.) in ethanol (15 c.c.) was heated at 60° for 30 min.; the quaternary picolinium bromide precipitated on addition of ether was treated with boiling water (50 c.c.) containing hydrogen sodium carbonate (4 g.). The precipitate crystallised from ethanol as grey-tinged prisms, m. p. 243°, which lost one mol. of water only on prolonged heating above 100° (Found : C, 80·0; H, 5·5. $C_{14}H_{11}ON$ requires C, 80·4; H, 5·3%).

Action of Bromine on 4-*Hydroxypropiophenone.*—(a) *Side-chain bromination.* Obtained as for the lower homologue, *α-bromo-4-hydroxypropiophenone* formed from aqueous acid colourless, lachrymatory needles, m. p. 98°, which gave a precipitate of aniline hydrobromide when heated with aniline (Found : C, 47·5; H, 4·1. $C_9H_9O_2Br$ requires C, 47·2; H, 3·9%). 3-Bromo-4-hydroxypropiophenone, m. p. 124° (Hoán and Buu-Hoï, *loc. cit.*), after treatment with boiling aniline, was recovered unchanged.

(b) *Nuclear bromination.* 3 : 5-*Dibromo-4-hydroxypropiophenone* (6·5 g.), obtained in the treatment of 4-hydroxypropiophenone (5 g.) with bromine (10·6 g.) in aqueous acetic acid, formed colourless needles, m. p. 114°, from the same solvent (Found : C, 35·0; H, 2·9. $C_9H_8O_2Br_2$ requires C, 35·1; H, 2·6%); this ketone was stable in aqueous potassium hydroxide, and treatment with methyl sulphate gave 3 : 5-*dibromo-4-methoxypropiophenone*, needles, m. p. 59° (from ethanol) (Found : C, 37·2; H, 3·2. $C_{10}H_{10}O_2Br_2$ requires C, 37·3; H, 3·1%). The *x* : *x'*-dibromo-4-hydroxypropiophenone, m. p. 100°, described by Goldzweig and Kaiser (*loc. cit.*) could be mainly converted into the same methyl ether, and contained a component with labile bromine (aniline test).

Preparation of Fluoro-ketones.—Friedel–Crafts acylations of *o*-fluoroanisole were performed with acid chlorides and aluminium chloride in carbon disulphide in the usual way; the methoxy-ketones were purified by vacuum-distillation and recrystallisation from ligroin, and were in general obtained in better yields (75—85%) than with anisole. The corresponding hydroxy-ketones were purified by vacuum-distillation and recrystallisation from aqueous acetic acid or aqueous ethanol, and were all colourless prisms; nuclear bromination of the fluorohydroxy-ketones was performed in aqueous acetic acid.

3-*Benzoylhexœstrol* [3-(3-*Benzoyl*-4-*hydroxyphenyl*)-4-p-*hydroxyphenylhexane*] (IV).—To a well-cooled solution of hexœstrol dimethyl ether (50 g.) and benzoyl chloride (25 g.) in redistilled nitrobenzene (200 c.c.), finely powdered aluminium chloride (25 g.) was added portion-wise; the mixture was kept at 5° overnight, then treated with ice, and the nitrobenzene removed by steam; the residue gave on vacuum-fractionation a portion, b. p. 305—308°/20 mm. (37 g.), which was a thick resin, giving on treatment with boiling pyridine hydrochloride 3-*benzoyl-hexœstrol*, crystallising as colourless needles, m. p. 201—202°, from benzene (Found : C, 80·5; H, 6·8. $C_{25}H_{24}O_3$ requires C, 80·6; H, 6·5%); the substance gave yellow alkaline solutions.

3-p-*Anisoylhexœstrol Dimethyl Ether.*—Similarly prepared by Friedel–Crafts reaction from

hexœstrol dimethyl ether (50 g.), anisoyl chloride (30 g.), and aluminium chloride (25 g.) in nitrobenzene (200 c.c.), this *ketone* formed colourless needles (60 g.), m. p. 112°, b. p. 328—330°/15 mm., from methanol (Found: C, 77·6; H, 7·5. $C_{28}H_{32}O_4$ requires C, 77·8; H, 7·4%).

4-*Hydroxy*-3 : 5-*di-iodopropiophenone*.—To a mixture of 4-hydroxypropiophenone (5 g.), yellow mercuric oxide (14·4 g.), and ethanol (100 c.c.), iodine (17 g.) was added in small portions with stirring; after the iodine had disappeared, the mixture was filtered by suction and the solid mass treated with dilute aqueous potassium hydroxide; after filtration, the alkaline solution was neutralised with hydrochloric acid, and the precipitate repeatedly recrystallised from benzene–ligroin. 4-*Hydroxy*-3 : 5-*di-iodopropiophenone* formed colourless needles, m. p. 124° (Found: C, 27·3; H, 2·1. $C_9H_8O_2I_2$ requires C, 26·9; H, 2·0%); 3 : 5-*di-iodo*-4-*methoxypropiophenone*, prepared by heating for 1 hr. the foregoing compound (2 g.) with methyl iodide (1 g.) and potassium hydroxide (0·3 g.) in ethanol (30 c.c.), formed colourless needles, m. p. 104°, from ethanol (Found: C, 29·0; H, 2·4. $C_{10}H_{10}O_2I_2$ requires C, 28·8; H, 2·4%).

4-*Hydroxy*-3 : 5-*di-iodobutyrophenone*, prepared from 4-hydroxybutyrophenone (10 g.), yellow mercuric oxide (26·3 g.), and iodine (31 g.) in ethanol, formed colourless needles, m. p. 106°, from aqueous acetic acid (Found: C, 29·0; H, 2·3. $C_{10}H_{10}O_2I_2$ requires C, 28·8; H, 2·4%); 3 : 5-*di-iodo*-4-*methoxybutyrophenone* formed colourless prisms, m. p. 79°, from ethanol (Found: C, 31·0; H, 3·0. $C_{11}H_{12}O_2I_2$ requires C, 30·7; H, 2·8%). 4-*Hydroxy*-3 : 5-*di-iodohexanophenone* formed colourless prisms, m. p. 69° (Found: C, 32·8; H, 3·0. $C_{12}H_{14}O_2I_2$ requires C, 32·4; H, 3·1%). 4-*Hydroxy*-3 : 5-*di-iodoheptanophenone* formed colourless needles, m. p. 50°, from ligroin (Found: C, 33·8; H, 3·2. $C_{13}H_{16}O_2I_2$ requires C, 34·1; H, 3·5%).

Friedel–Crafts Reactions with Diphenyl Oxide.—(a) *With propionyl chloride*. The reaction of propionyl chloride (1·5 mol.) with diphenyl oxide (1 mol.) in carbon disulphide in the presence of aluminium chloride (1·2 mol.) gave, in addition to 4-propionyldiphenyl oxide, b. p. 210—212°/13 mm., crystallising as colourless leaflets, m. p. 36°, from methanol (Dilthey *et al.*, *J. pr. Chem.*, 1927, **117**, 359, described this substance as a liquid), some 4 : 4′-*dipropionyldiphenyl oxide*, b. p. 270—272°/15 mm., crystallising as colourless needles, m. p. 100°, from methanol (Found: C, 76·5; H, 6·5. $C_{18}H_{18}O_3$ requires C, 76·6; H, 6·4%).

(b) *With higher aliphatic acid chlorides*. 4-iso*Butyryldiphenyl oxide* formed a pale yellow oil, b. p. 223—224°/21 mm., n_D^{23} 1·5741 (Found: C, 80·0; H, 6·9. $C_{16}H_{16}O_2$ requires C, 80·0; H, 6·7%); 4-*hexanoyldiphenyl oxide* had b. p. 236—238°/15 mm., and formed lustrous leaflets, m. p. 39°, from ligroin (Found: C, 80·5; H, 7·5. $C_{18}H_{20}O_2$ requires C, 80·6; H, 7·5%); 4-*octanoyldiphenyl oxide*, b. p. 250—252°/15 mm., formed silky needles, m. p. 35°, from ligroin (Found: C, 81·3; H, 8·2. $C_{20}H_{24}O_2$ requires C, 81·1; H, 8·1%).

Preparation of Indoles.—The 2-*arylindoles* listed in Table 3 were prepared by heating at 110—120° a mixture of phenylhydrazine and the appropriate ketone until steam ceased to be evolved, and boiling for a few minutes the crude hydrazone thus formed with acetic acid saturated with hydrogen chloride; the precipitate obtained on addition of water was collected, washed with water, and recrystallised several times from ligroin (for the phenolic compounds) or ethanol (for the methoxy-compounds). These indoles generally retained crystallisation-solvents very strongly, and must be carefully dried in vacuum for analysis.

4 : 4′-*Di*-(3-*methyl*-2-*indolyl*)*diphenyl Oxide* (III).—Prepared as above from phenylhydrazine (2 mol.) and 4 : 4′-dipropionyldiphenyl oxide (1 mol.), this *ether* crystallised as colourless prisms, m. p. 210°, from ethanol, giving a deep violet picrate (Found: N, 6·4. $C_{30}H_{24}ON_2$ requires N, 6·5%).

The authors thank Sir Charles Harington, Director, National Institute for Medical Research (London), for having had 4-hydroxy-3 : 5-di-iodopropiophenone tested in his Institute, and Laroche-Navarron Laboratories (Paris) for a Fellowship (D.L.).

The Radium Institute, University of Paris. [*Received, November* 19*th*, 1953.]

*Syntheses from Phthalimido-acids. Part IV.** p-*Glycylaminobenzoic Acid and Derivatives.*

By F. E. King, J. W. Clark-Lewis, D. A. A. Kidd, and G. R. Smith.

[Reprint Order No. 4831.]

p-(Phthalylglycylamino)benzoic acid has been prepared from *p*-aminobenzoic acid and phthalylglycyl chloride or its ethyl carbonic anhydride, and *p*-(formylglycylamino)benzoic acid by the azide or mixed anhydride method from formylglycine. By the action of hydrazine on ethyl *p*-(phthalylglycylamino)benzoate, and of ethanolic hydrogen chloride on *p*-(formylglycylamino)benzoic acid, ethyl *p*-glycylaminobenzoate was obtained, which was further hydrolysed to *p*-glycylaminobenzoic acid. *p*-Glycylaminobenzoyl-L-glutamic acid has been synthesised *via* its phthalyl derivative from *p*-aminobenzoyl-L-glutamic acid.

p-Glycylaminobenzoic acid was obtained by Tropp (*Ber.*, 1928, **61**, 1431) from *p*-chloroacetamidobenzoic acid and aqueous ammonia. In meeting the requirements of biochemical experiments we have investigated the synthesis of this compound by general methods developed since its description by Tropp. These include the use of phthalylated compounds, first applied to simple peptide synthesis by Sir Robert Robinson and one of us (see King and Kidd, *Nature*, 1948, **162**, 776; *J.*, 1949, 3315; cf. Sheehan and Frank, *J. Amer. Chem. Soc.*, 1949, **71**, 1856), and of the mixed (carbonic) anhydride coupling procedure (Boissonnas, *Helv. Chim. Acta*, 1951, **34**, 874; Vaughan, *J. Amer. Chem. Soc.*, 1951, **73**, 3547; 1952, **74**, 6137; Wieland and Bernhard, *Annalen*, 1951, **572**, 190). It was also prepared *via* the *N*-formyl compound from *N*-formylglycine (D. A. A. Kidd, Thesis, Oxford, 1950), an example of a method of synthesis recently described by Waley for three other dipeptides (*Chem. and Ind.*, 1953, 107).

p-(Phthalylglycylamino)benzoic acid was prepared from phthalylglycyl chloride by direct condensation with *p*-aminobenzoic acid in aqueous solution (yield 77%) or through the ethyl carbonic anhydride (65%). The corresponding ethyl ester was obtained from phthalylglycyl chloride and ethyl *p*-aminobenzoate (yield 87%), or by treating *p*-(phthalylglycylamino)benzoic acid with 1·5% hydrogen chloride in alcohol; the use of boiling ethanol saturated with hydrogen chloride resulted in alcoholysis to phthalylglycine ethyl ester and ethyl *p*-aminobenzoate. Removal of the phthalyl group with ethanolic hydrazine gave ethyl *p*-glycylaminobenzoate, conveniently isolated as its hydrochloride (72%). *p*-Ethoxycarbonyl(hydroxyimino)acetanilide, obtained from *p*-aminobenzoic acid, chloral, and hydroxylamine, as in Sandmeyer's synthesis of hydroxyiminoacetanilide (*Helv. Chim. Acta*, 1919, **2**, 237; *Org. Synth.*, 1925, **5**, 71), was also used in a preparation of the *p*-glycylaminobenzoate, but catalytic hydrogenation of the hydroxyimino-compound yielded only 18% of the primary amine.

No product corresponding to the acid chloride (or oxazolone hydrochloride) was obtainable from formylglycine, *e.g.*, with thionyl chloride or with phosphorus pentachloride in acetyl chloride or other solvents. The formamido-acid also failed to give any recognisable compound with ethyl *p*-aminobenzoate when a mixture of the two substances was treated with phosphorus trichloride in boiling benzene, a coupling procedure devise by Süs (*Annalen*, 1951, **572**, 96). On the other hand, ethyl *p*-benzoyl- and *p*-acetyl-glycylaminobenzoate were successfully formed in this way (yields 73% and 64% respectively), the acetyl ester and related acid being also obtained (yields 52%) from ethyl *p*-aminobenzoate and from *p*-aminobenzoic acid by the action of acetylglycyl ethyl carbonic anhydride. The preparation of formylglycine derivatives was possible, however, when *N*-formylglycine was converted through the hydrazide into formylglycine azide, which, having given with aniline the anilide, was then used to yield *p*-(formylglycylamino)benzoic acid.

Removal of the protecting formyl group without disturbance of the peptide link depends on the sensitivity of formamides to ethanolic hydrogen chloride, a property

* Part III, *J.*, 1951, 2976.

utilised in the preparation of ββ-diethoxyalanine and its derivatives (cf. Brown, "The Chemistry of Penicillin," Oxford Univ. Press, 1949, p. 492). After treatment with this reagent, *p*-(formylglycylamino)benzoic acid gave the dipeptide ester, identical with the material obtained from ethyl *p*-(phthalylglycylamino)benzoate, and hydrolysed with cold aqueous alkali to the *p*-(glycylamino)benzoic acid (Tropp, *loc. cit.*) (yield from the formyl acid, 38%).

p-(Formylglycylamino)benzoic acid (47%) was also prepared by the mixed carbonic anhydride method from *p*-aminobenzoic acid, but with ethyl *p*-aminobenzoate, only ethyl *p*-ethoxycarbonylaminobenzoate (55%) was obtained. As there appeared to be no reason to suspect the presence of unchanged ethyl chloroformate in the mixture before the addition of the aminobenzoate, this result is attributed to the abnormal behaviour of the mixed anhydride in yielding the cation EtO_2C^+ instead of the expected species $H{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CO^+$.

The *N*-acyl derivatives of *p*-glycylaminobenzoic acid proved unsuitable for the synthesis of a typical derivative of the dipeptide, *i.e.*, *p*-glycylaminobenzoyl-L-glutamic acid. Thus ethyl *p*-(formylglycylamino)benzoate failed to react with hydrazine, thus excluding the azide method of condensation, and its triethylamine salt was too insoluble to allow of the preparation of the mixed carbonic anhydride. The phthalyldipeptide, on the other hand, appears to form anhydrides with both ethyl and *iso*butyl chlorocarbonate, but it was recovered unchanged after treatment of the supposed anhydrides both with L-glutamic acid and with glycine (experiments by Mr. R. Wade). The desired tripeptide was therefore prepared from phthalylglycyl chloride and *p*-aminobenzoyl-L-glutamic acid, the intermediate phthalyl compound being hydrolysed with hydrazine.

Experimental

p-(*Phthalylglycylamino*)*benzoic Acid.*—(i) A solution of *p*-aminobenzoic acid (2·74 g.) in water (50 c.c.) containing sodium carbonate (1·1 g., 1 equiv.) was cooled in an ice-bath and stirred during the simultaneous addition in 1 hr. of solutions of phthalylglycyl chloride (4·46 g.) in dioxan (50 c.c.), and sodium carbonate (1·1 g.) in water (50 c.c.). After a further hour the solution was acidified (Congo-red) with 2N-hydrochloric acid, and the white precipitate collected and crystallised from aqueous 2-ethoxyethanol or aqueous ethanol. p-(*Phthalylglycylamino*)-*benzoic acid* separated in matted hair-like needles (5 g., 77%), m. p. 331—332° (decomp.), raised by recrystallisation to 332—333° (decomp.) (Found: C, 62·8; H, 4·0; N, 8·9. $C_{17}H_{12}O_5N_2$ requires C, 63·0; H, 3·7; N, 8·6%).

(ii) A solution of phthalylglycine (2·05 g.) in dry dioxan (20 c.c.) containing triethylamine (1·4 c.c., 1 equiv.) was cooled to 10° and stirred during the addition of ethyl chloroformate (0·96 c.c., 1 equiv.). Triethylamine hydrochloride was precipitated and 10 min. later the mixture was treated with a solution of *p*-aminobenzoic acid (1·37 g.) in aqueous N-sodium hydroxide (10 c.c., 1 equiv.). After effervescence had ceased, a small volume of N-sodium hydroxide was added and the solution thrice extracted with ether. The aqueous phase was acidified (Congo-red) with 5N-hydrochloric acid, and the precipitated *p*-(phthalylglycylamino)benzoic acid (2·12 g., 65%), m. p. 330° (decomp.), was collected and crystallised from aqueous ethanol from which it separated in matted needles.

The action of aqueous hydrazine solution on *p*-(phthalylglycylamino)benzoic acid dissolved in boiling ethanol or in cold aqueous sodium carbonate solution appeared to remove the protecting group, but owing to the low solubility of *p*-glycylaminobenzoic acid in hydrochloric acid it could not be separated from the accompanying phthalhydrazide.

Ethyl p-(*Phthalylglycylamino*)*benzoate.*—(i) A solution of ethyl *p*-aminobenzoate (13·2 g., 2 equivs.) in dry chloroform (50 c.c.) was stirred during the dropwise addition in 2 hr. of phthalylglycyl chloride (8·92 g.) likewise dissolved in chloroform (50 c.c.). Additional solvent was introduced during the reaction to allow efficient stirring to be maintained. After a further hour, the chloroform was evaporated under reduced pressure, and the residue washed with 2N-hydrochloric acid and with water, the *ethyl* p-(*phthalylglycylamino*)*benzoate* crystallising from ethanol as glistening plates or rods (12·3 g., 87%) (Found: C, 64·8; H, 4·2; N, 8·4. $C_{19}H_{16}O_5N_2$ requires C, 64·8; H, 4·6; N, 8·0%).

(ii) A suspension of *p*-(phthalylglycylamino)benzoic acid (1·0 g.) in anhydrous ethanol (50 c.c.) containing hydrogen chloride (1·5%) was heated under reflux until dissolution was almost complete. The liquid was filtered and then cooled, whereupon ethyl *p*-(phthalylglycylamino)benzoate (0·44 g.) separated in plates, m. p. 207—208°, raised by recrystallisation from

ethanol to 212° (mixed m. p. 212°). When the filtrate was evaporated and the residue crystallised from ethanol a further quantity (0·20 g.) of the ester, m. p. 210°, was obtained (total 59%).

A suspension of *p*-(phthalylglycylamino)benzoic acid (1·0 g.) in absolute ethanol (50 c.c.) saturated with hydrogen chloride was heated under reflux for 1 hr. The solvent was then removed and the residue washed with dilute hydrochloric acid and with water. The undissolved solid consisted of phthalylglycine ethyl ester and crystallised from aqueous ethanol in rods (0·63 g., 88%), m. p. 108°, raised by recrystallisation to 110°, mixed m. p. with an authentic specimen 111°. The hydrochloric acid washings gave, when basified, ethyl *p*-aminobenzoate which after crystallisation from aqueous ethanol had m. p. and mixed m. p. 88°.

Ethyl p-*Glycylaminobenzoate*.—(i) A solution of ethyl *p*-(phthalylglycylamino)benzoate (14·1 g.) in ethanol (560 c.c.) was treated with aqueous hydrazine (4 c.c., 33·2%, 1·04 equivs.) and heated under reflux for 1 hr. The pale yellow solution was evaporated to dryness and after treatment with 2N-hydrochloric acid the mixture was set aside at 0° for several hours. The precipitate was collected and repeatedly triturated with water containing a little hydrochloric acid. The filtrates were combined and evaporated under reduced pressure at 45°, long needles of *ethyl* p-*glycylaminobenzoate hydrochloride* (7·5 g., 72%), m. p. 238—240° (decomp.), separating during the evaporation. Precipitation of the hydrochloride from ethanol with anhydrous ether gave needles, m. p. 244—246° (decomp.) (Found: C, 51·2; H, 5·8; N, 10·7. $C_{11}H_{14}O_3N_2$,HCl requires C, 51·0; H, 5·8; N, 10·8%).

The hydrochloride was dissolved in a little water and treated with aqueous sodium carbonate. Crystallisation of the heavy white precipitate from water afforded *ethyl* p-*glycylaminobenzoate monohydrate* as long rods, m. p. 96—97° (Found: C, 55·0; H, 7·0; N, 11·8. $C_{11}H_{14}O_3N_2$,H_2O requires C, 55·0; H, 6·7; N, 11·7%). The anhydrous *ester*, m. p. 88·5—89°, was obtained when the monohydrate was dried in a vacuum at 60° (Found: C, 59·7; H, 6·4; N, 12·5. $C_{11}H_{14}O_3N_2$ requires C, 59·5; H, 6·3; N, 12·6%).

(ii) A mixture of *p*-ethoxycarbonyl(hydroxyimino)acetanilide (below) (2·64 g.), palladium–charcoal (0·7 g.), palladium chloride (0·3 g.), hydrochloric acid (35%, 2·5 c.c.), and ethanol (50 c.c.) was shaken in hydrogen (20 atm.). The reddish-brown product obtained by evaporation was extracted with 2N-hydrochloric acid, and the extract concentrated. The crystalline material which separated during the evaporation was collected and dissolved in water, and the solution made alkaline. The brown flocculent precipitate was removed and extracted with boiling water. When the solution was cooled, ethyl *p*-glycylaminobenzoate monohydrate (0·50 g., 18%) separated as rods, m. p. 96—97° (Found: N, 11·6%).

p-*Ethoxycarbonyl*(*hydroxyimino*)*acetanilide*.—To a solution of chloral hydrate (9 g.) in water (120 c.c.) were added crystalline sodium sulphate (130 g.), ethyl *p*-aminobenzoate (8·26 g.) dissolved in water (60 c.c.) containing the necessary volume of concentrated hydrochloric acid for solution, and hydroxylamine hydrochloride (11 g. in 50 c.c. of water). The mixture was rapidly heated and boiled for 2 min., an orange oil separating. When cooled, the oil solidified, and by crystallising it from boiling water p-*ethoxycarbonyl*(*hydroximino*)*acetanilide* (3·9 g., 33%) was obtained as pale yellow plates, m. p. 148—149°. Recrystallisation from water (charcoal) yielded colourless needles, m. p. 173—175°, possibly a stereoisomer of the product of m. p. 148—149° (Found: C, 56·0; H, 5·3; N, 12·1. $C_{11}H_{12}O_4N_2$ requires C, 55·9; H, 5·1; N, 11·9%).

Ethyl p-(*Benzoylglycylamino*)*benzoate*.—(i) A suspension of benzoylglycine (3·0 g.) in dry benzene (100 c.c.) containing ethyl *p*-aminobenzoate (3·2 g.) was treated with freshly distilled phosphorus trichloride (1·5 c.c.), heat being evolved and a gelatinous solid precipitated. The mixture was heated under reflux on a steam-bath for 2 hr. while hydrogen chloride was continuously evolved. The solvent was then evaporated under reduced pressure and the residue washed with aqueous sodium carbonate. The undissolved material was dried and crystallised from ethyl acetate, *ethyl* p-(*benzoylglycylamino*)*benzoate* (4·0 g., 73%) separating as felted needles, m. p. 169—170° raised by recrystallisation to 170—171°. A further quantity (0·45 g.), m. p. 169—170°, was obtained by concentration of the mother-liquors (total yield 81%) (Found: C, 66·4; H, 5·3; N, 8·7. $C_{18}H_{18}O_4N_2$ requires C, 66·3; H, 5·6; N, 8·6%).

(ii) A solution of ethyl *p*-glycylaminobenzoate (0·3 g.) in pure dry chloroform (10 c.c.) was treated with excess of benzoyl chloride and triethylamine and shaken for 15 min. The solvent was removed *in vacuo* and the residue washed with dilute hydrochloric acid, aqueous sodium carbonate, and water. The residue of ethyl *p*-(benzoylglycylamino)benzoate crystallised from ethyl acetate in felted needles, m. p. and mixed m. p. 170°.

Ethyl p-(*Acetylglycylamino*)*benzoate*.—(i) A suspension of acetylglycine (1·2 g.) in benzene (100 c.c.) containing ethyl *p*-aminobenzoate (1·92 g.) was treated with freshly distilled phosphorus

trichloride (0·9 c.c.), and the mixture heated under reflux on a steam-bath for 2 hr. The solvent was then evaporated under reduced pressure and the residue extracted with aqueous sodium carbonate. The residue of *ethyl* p-(*acetylglycylamino*)*benzoate* crystallised from ethyl acetate or moist ethanol (charcoal) in plates (1·7 g., 64%), m. p. 224° (Found : C, 59·1; H, 6·1; N, 10·7. $C_{13}H_{16}O_4N_2$ requires C, 59·1; H, 6·1; N, 10·6%).

(ii) A solution of acetylglycine (1·17 g.) in dry chloroform (20 c.c.) containing triethylamine (1·4 c.c.) was cooled to 0° and stirred during the addition of ethyl chloroformate (0·96 c.c.). After the solution had been kept at 0° for a further 10 min., a solution of ethyl *p*-aminobenzoate (1·65 g.) in chloroform (20 c.c.) was added. Effervescence was slight and the solution was left overnight at room temperature. The precipitate was collected and crystallised from ethyl acetate (1·17 g., 44%), separating as plates, m. p. and mixed m. p. 224°. A further quantity (0·2 g.) was obtained by concentration of the chloroform solution (total yield 52%).

p-(*Acetylglycylamino*)*benzoic Acid.*—A solution of acetylglycine (1·17 g.) in pure dry dioxan (10 c.c.) containing triethylamine (1·4 c.c.) was cooled to 10° and stirred during the addition of ethyl chloroformate (0·96 c.c.). Triethylamine hydrochloride was precipitated immediately and after a further 10 min. at 10° a solution of *p*-aminobenzoic acid (1·37 g.) in N-sodium hydroxide (10 c.c.) was added. When effervescence had ceased aqueous sodium hydroxide was added and the solution was thrice extracted with ether. The aqueous phase was acidified with 5N-hydrochloric acid and stored at 0° for several hours. The precipitate of p-(*acetylglycylamino*)*benzoic acid* (1·24 g., 52%) crystallised from aqueous ethanol or aqueous dioxan as plates, m. p. varying from 260° to 270° (decomp.) with rate of heating (Found : C, 56·2; H, 5·3; N, 11·5. $C_{11}H_{12}O_4N_2$ requires C, 56·0; H, 5·1; N, 11·8%).

Formylglycine Hydrazide.—A solution of formylglycine ethyl ester (20·2 g.) in ethanol (50 c.c.) was treated with hydrazine hydrate (15 c.c. of 60%), an exothermic reaction taking place. After some hours the *hydrazide* slowly separated in colourless rectangular prisms (13·6 g., 74%), which after crystallisation from ethanol had m. p. 130° (Found : C, 31·2; H, 5·7; N, 35·5. $C_3H_7O_2N_3$ requires C, 30·8; H, 6·0; N, 35·9%).

Formylglycine Anilide.—A solution of formylglycine hydrazide (4 g.) in N-hydrochloric acid (40 c.c.) at 0° was stirred during the addition of 1 mol. of aqueous sodium nitrite (10%). The solution was neutralised with sodium carbonate and then treated with aniline (10 c.c.). Stirring was continued for 2 hr., after which the precipitate was collected, washed with dilute hydrochloric acid, and crystallised from water. *Formylglycine anilide* was thus obtained in plates, m. p. 152° (Found : C, 60·5; H, 5·7; N, 15·9. $C_9H_{10}O_2N_2$ requires C, 60·5; H, 5·7; N, 15·7%).

p-(*Formylglycylamino*)*benzoic Acid.*—(i) *N*-Formylglycine hydrazide (5 g.) in N-hydrochloric acid (50 c.c.) was converted into the azide, and the solution made just alkaline and treated at 0° with *p*-aminobenzoic acid (5·4 g.) dissolved in aqueous sodium carbonate (50 c.c. of 5%) added during 1 hr. The addition of 5N-hydrochloric acid then precipitated the p-(*formylglycylamino*)*benzoic acid* as a cream-coloured solid (4·4 g.) which when collected crystallised from a very large volume of water in small glistening prisms, decomp. 253—254° (Found : C, 53·9; H, 4·6; N, 12·2. $C_{10}H_{10}O_4N_2$ requires C, 54·0; H, 4·5; N, 12·6%).

(ii) A solution of formylglycine (2·06 g.) in acetone (30 c.c.) containing triethylamine (2·8 c.c.) was cooled to 0° and stirred during the addition of ethyl chloroformate (1·92 c.c.). After a further 10 min. at 0°, *p*-aminobenzoic acid (2·74 g.) in aqueous N-sodium hydroxide (20 c.c.) was added, and when the reaction ceased the solution was acidified with 5N-hydrochloric acid and the acetone was evaporated under reduced pressure. The precipitate of *p*-(formylglycylamino)benzoic acid (2·1 g., 47%) was collected after 15 hr. at 0° ; it crystallised from water or from aqueous dioxan in prisms, decomp. *ca.* 250° depending on the rate of heating.

The mixed anhydride from *N*-formylglycine and ethyl chloroformate prepared as in (ii) and kept at 0° for 10 min. was treated with a solution of ethyl *p*-aminobenzoate (3·3 g.) in acetone. No effervescence was observed, and later, when the solution was evaporated to dryness and the residue washed with dilute hydrochloric acid and aqueous sodium carbonate, the product was found to be ethyl *p*-(ethoxycarbonylamino)benzoate (2·73 g., 55%), m. p. 128—130°. Crystallised from aqueous ethanol it formed plates, m. p. 130° alone or with an authentic specimen. The same product was obtained when chloroform was used as solvent.

p-*Glycylaminobenzoic Acid.*—A suspension of the formyl-dipeptide (1·5 g.) in ethanol (15 c.c.) saturated at 0° with dry hydrogen chloride was momentarily warmed to boiling and set aside for 4—5 hr. The microcrystalline ester hydrochloride was collected, dissolved in a little cold water, and treated with 2·5N-sodium hydroxide (10 c.c.). The voluminous precipitate was then redissolved by the addition of a little acetone, and the solution set aside for

30 min. to complete hydrolysis of the ester. Addition of acetic acid slowly precipitated *p*-glycylaminobenzoic acid (0·5 g.) which crystallised from hot water as needles, m. p. 300° (decomp.), consisting either of a *dihydrate* (Found: C, 47·2; H, 6·1; N, 12·3. $C_9H_{10}O_3N_2,2H_2O$ requires C, 47·0; H, 6·1; N, 12·2%) or of the monohydrate (cf. Tropp, *loc. cit.*) (Found: C, 50·5; H, 5·7; N, 13·2. Calc. for $C_9H_{10}O_3N_2,H_2O$: C, 50·9; H, 5·7; N, 13·2. Found, in specimen dried at 150° *in vacuo*: C, 55·6; H, 5·5; N, 14·1. Calc. for $C_9H_{10}O_3N_2$: C, 55·7; H, 5·2; N, 14·4%).

Alternatively, the ester hydrochloride was dissolved in water and neutralised with aqueous sodium hydroxide. The liberated solid was washed with water and recrystallised from aqueous ethanol, and thus afforded colourless felted needles of ethyl *p*-glycylaminobenzoate monohydrate, m. p. 96—97°, described above (Found, in the dried material: C, 59·1; H, 6·4; N, 12·1%).

Ethyl p-(*Formylglycylamino*)*benzoate*.—Formylglycine hydrazide (9·4 g.), dissolved in a mixture of water (10 c.c.) and concentrated hydrochloric acid (7·1 c.c.), was treated with acetic acid (15 c.c.) and cooled to 0°. Aqueous sodium nitrite (7 g. in 11 c.c.) was run in and the solution immediately extracted four times with chilled ethyl acetate. The combined extracts were washed with cold dilute aqueous sodium hydrogen carbonate and water, dried ($MgSO_4$), and added to an ethereal solution of ethyl *p*-aminobenzoate (12·2 g.). Within 2 hr., the *ethyl* p-(*formylglycylamino*)*benzoate* began to separate and after 16 hr. at 0° it was collected and crystallised from aqueous ethanol. The ester (5·4 g.), m. p. 175°, separated in small needles, m. p. after further crystallisation 178° (Found: C, 58·0; H, 5·6; N, 11·3. $C_{12}H_{14}O_4N_2$ requires C, 57·6; H, 5·6; N, 11·2%). An alternative procedure, in which the azide solution was not extracted, but was instead neutralised and added to an acetone solution of ethyl *p*-aminobenzoate under slightly alkaline conditions, gave a poorer yield (13%) of the formyl-dipeptide ester.

The ester was recovered unchanged after 2 hours' refluxing in ethanol solution with 100% hydrazine hydrate. When the ester (5·25 g.) was heated under reflux with 100% hydrazine hydrate (20 c.c.) in the absence of any other solvent, *p*-aminobenzhydrazide (2·8 g.), crystallising from ethanol in long needles, m. p. 220° (decomp.) [lit., m. p. 220° (decomp.)], was obtained (Found: C, 55·8; H, 6·0; N, 27·8. Calc. for $C_7H_9ON_3$: C, 55·6; H, 6·0; N, 27·8%).

p-(*Phthalylglycylamino*)*benzoyl-*L*-glutamic Acid*.—Aqueous sodium hydroxide (30 c.c. of 2%) and phthalylglycyl chloride (2·9 g.) (Harwood and Johnson, *J. Amer. Chem. Soc.*, 1933, **55**, 4178) in dioxan (30 c.c.) were added simultaneously with stirring to a solution of *p*-aminobenzoyl-L-glutamic acid (3·5 g.) (King, Acheson and Spensley, *J.*, 1949, 1401) in aqueous sodium hydroxide (1·1 g. in 30 c.c.) at room temperature during ½ hr. After 2 hr. the mixture was acidified with 5N-hydrochloric acid, this precipitating an oil which rapidly solidified and then separated from hot water as a gelatinous mass. The dried product formed a nearly white powder (2·7 g.), m. p. 178°. Recrystallisation gave the persistently gelatinous pure *phthalyl-tripeptide*, m. p. 189—190°, as a monohydrate (Found, in material dried at 15°: C, 56·4; H, 4·4; N, 8·6. $C_{22}H_{19}O_8N_3,H_2O$ requires C, 56·1; H, 4·5; N, 8·9%. Found, in material dried at 140° in a vacuum: C, 58·1; H, 4·3; N, 9·3. $C_{22}H_{19}O_8N_3$ requires C, 58·3; H, 4·2; N, 9·3%).

p-(Phthalylglycylamino)benzoic acid was dissolved in *NN*-dimethylformamide and treated with triethylamine and then with either ethyl or *iso*butyl chloroformate below 5°. A solution of L-glutamic acid in N-sodium hydroxide, added 10 min. later, caused effervescence but the product obtained by acidifying the ethyl acetate-washed aqueous liquid consisted of *p*-(phthalylglycylamino)benzoic acid, fine needles from aqueous 2-ethoxyethanol, m. p. 330° (decomp.). The phthalyl-dipeptide failed to react with glycine under similar conditions.

p-*Glycylaminobenzoyl-*L*-glutamic Acid*.—A solution of the phthalyl-tripeptide (2 g.) in aqueous sodium carbonate (0·5 g. in 15 c.c.) was left to react with hydrazine hydrate (0·25 g.) for 24 hr. at room temperature, and then exactly neutralised with hydriodic acid. After removal of the phthalhydrazide, the filtrate was evaporated to dryness and the gummy residue triturated with acetone. The sparingly soluble white powder crystallised slowly at 0° from an aqueous solution rendered turbid with ethanol at room temperature, the pure *tripeptide* affording fine colourless needles which decomposed with effervescence at 252—253° (Found: C, 52·3; H, 5·5; N, 13·3. $C_{14}H_{17}O_6N_3$ requires C, 52·0; H, 5·3; N, 13·0%).

Awards of a Medical Research Council Studentship (to D. A. A. K.) and a maintenance allowance from the Department of Scientific and Industrial Research (to G. R. S.) are gratefully acknowledged.

THE UNIVERSITY, NOTTINGHAM. [*Received, November 25th*, 1953.]

Syntheses from Phthalimido-acids. Part V. Amides of Glycine,* DL-*Alanine, and* L-*Glutamic Acid with Amphetamine, Benzocaine, and Procaine.*

By F. E. King, J. W. Clark-Lewis, and G. R. Smith.

[Reprint Order No. 4832.]

Phthalylglycyl derivatives of amphetamine (2-phenyl*iso*propylamine) and of procaine (2-diethylaminoethyl *p*-aminobenzoate), and ethyl *p*-(phthalyl-DL-alanylamino)benzoate (phthalyl-DL-alanylbenzocaine) have been synthesised. The reactions of benzocaine and of amphetamine with phthalyl-DL-glutamic anhydride resemble those of ammonia, ethanol, etc. (cf. King and Kidd, *J.*, 1949, 3315; King, Jackson, and Kidd, *J.*, 1951, 243), in yielding γ-compounds. The free amino-acid amides have been prepared from the phthalylated products by treatment with hydrazine.

Simple aminoacyl derivatives of the drugs amphetamine, procaine, and benzocaine were required for pharmacological investigation. The selected amino-acids, *i.e.* glycine, DL-alanine, and L-glutamic acid, were brought into reaction with these amines in the form of their phthalyl compounds, the final stage, namely, removal of the phthalyl group, being accomplished with hydrazine as in previous work of this nature, *e.g.*, Part IV.*

The condensation of phthalylglycyl chloride with amphetamine in chloroform–aqueous alkali gave phthalylglycine 2-phenyl*iso*propylamide (yield 76%), glycylamphetamine being isolated as hydrochloride (66%) after hydrolysis of the phthalyl compound with hydrazine in boiling alcohol. Similarly, procaine gave 2-diethylaminoethyl *p*-(phthalylglycylamino)benzoate (yield of hydrochloride, 84%), from which glycylprocaine was obtained as a dihydrochloride after hydrazine treatment. Ethyl *p*-(phthalyl-DL-alanylamino)benzoate (80%) was prepared from phthalyl-DL-alanyl chloride and benzocaine, the product of its hydrolysis with hydrazine being obtained as a crystalline hydrochloride (69%). Phthalyl-DL-alanylprocaine on the other hand was a sticky solid characterised by its picrate.

Phthalyl-DL-glutamic anhydride reacted with ethyl *p*-aminobenzoate (benzocaine) dissolved in chloroform either at room temperature or at the boiling point, yielding up to 93% of ethyl *p*-(phthalyl-DL-glutamylamino)benzoate. Its representation as the γ-derivative follows from the results of similar experiments with ammonia, glycine, ethyl glutamate, and methanol (King and Kidd, *J.*, 1949, 3315; King, Jackson, and Kidd, *J.*, 1951, 243), and from the ninhydrin analysis of the α-amino-carboxy-group (Van Slyke, MacFadyen, and Hamilton, *J. Biol. Chem.*, 1941, **141**, 671) in the ethyl *p*-DL-glutamylaminobenzoate (yield 68%) obtained by hydrolysis of the aqueous sodium salt with hydrazine at room temperature (King and Kidd, *loc. cit.*). *p*-(Phthalyl-γ-DL-glutamylamino)benzoic acid (84%) was prepared by heating a mixture of phthalyl-DL-glutamic anhydride and *p*-aminobenzoic acid in dioxan. The product of a similar experiment with the anhydride and amphetamine in chloroform was a gum but crystalline DL-glutamic acid γ-2-phenyl*iso*propylamide (overall yield 64%) was obtained when it was hydrolysed in the cold with hydrazine.

Experimental

Phthalylglycine 2-Phenylisopropylamide.—2-Phenyl*iso*propylamine sulphate (3 g., 1 mol.) was dissolved in water (30 c.c.) and treated with 40% aqueous sodium hydroxide (3·3 c.c., 4 mols.) and chloroform (30 c.c.), the mixture being stirred during the dropwise addition in 15 min. of a chloroform solution (15 c.c.) of phthalylglycyl chloride (3·64 g., 2 mols.). The chloroform phase was then separated, washed free from alkali, and evaporated to dryness under reduced pressure. The residue of *phthalylglycine 2-phenylisopropylamide* crystallised from aqueous ethanol in rods (4·0 g., 76%), m. p. 167° (Found : C, 70·8; H, 5·4; N, 8·5. $C_{19}H_{18}O_3N_2$ requires C, 70·8; H, 5·6; N, 8·7%). Alternatively, amphetamine sulphate dissolved in a similar quantity of alkali (4·5%) was vigorously shaken during the addition of a solution of phthalylglycyl chloride (2 mols.) in dioxan. The white crystalline mass was collected and

* Part IV, preceding paper.

crystallised from aqueous ethanol, thereby giving rods (43%), m. p. 167°. In more concentrated alkali (10%) the precipitate first formed redissolved on being shaken, presumably owing to formation of the phthalamic acid. Acidification yielded a gum which, however, crystallised from aqueous alcohol and then had m. p. and mixed m. p. 167°.

Glycine 2-Phenylisopropylamide Hydrochloride.—A solution of phthalylglycine 2-phenyl-*iso*propylamide (12·88 g.) in ethanol (400 c.c.) was heated with aqueous hydrazine (4 c.c., 33·2%, 1·04 equivs.) under reflux for 1 hr. The solution, which became faintly yellow and deposited a small quantity of white solid, was evaporated to dryness under reduced pressure and the residue extracted with N-hydrochloric acid (100 c.c.) and finally with a little water. The combined extracts were evaporated at 45° (reduced pressure) and the crystalline residue, after being dried in a vacuum-desiccator, was dissolved in the minimum of ethanol. Addition of anhydrous ether precipitated glistening plates of *glycine 2-phenylisopropylamide hydrochloride* (6 g., 66%), m. p. 180°, raised by two crystallisations from *iso*propanol–light petroleum (b. p. 80—100°) to 192—193° (Found: C, 57·9; H, 7·2; N, 12·4. $C_{11}H_{16}ON_2$,HCl requires C, 57·6; H, 7·4; N, 12·3%).

2-Diethylaminoethyl p-(*Phthalylglycylamino*)*benzoate.*—A solution of 2-diethylaminoethyl *p*-aminobenzoate (4·74 g.) in chloroform (20 c.c.) at 0° was stirred during the addition in 1 hr. of a chloroform solution (50 c.c.) of phthalylglycyl chloride (4·46 g.). Solid slowly separated, and next morning the product was collected and crystallised from 2-ethoxyethanol, thus giving *2-diethylaminoethyl* p-(*phthalylglycylamino*)*benzoate hydrochloride* as plates (7·7 g., 84%), m. p. 224—228° (Found: C, 60·5; H, 5·8; N, 9·2. $C_{23}H_{25}O_5N_3$,HCl requires C, 60·1; H, 5·7; N, 9·1). Mixing aqueous solutions of sodium picrate and of the hydrochloride gave the *picrate* which crystallised from ethanol or aqueous ethanol as yellow needles, m. p. 220° (decomp.) (Found: C, 52·8; H, 4·4; N, 12·9. $C_{23}H_{25}O_5N_3$,$C_6H_3O_7N_3$ requires C, 53·3; H, 4·3; N, 12·9%). The addition of aqueous sodium carbonate to the hydrochloride liberated an oil which soon solidified and crystallised from methanol, giving prisms consisting of the *2-diethylaminoethyl* p-(*phthalylglycylamino*)*benzoate monohydrate*, m. p. 144—146° (Found: C, 62·7; H, 6·0; N, 9·8; loss, 4·1. $C_{23}H_{25}O_5N_3$,H_2O requires C, 62·5; H, 6·1; N, 9·5; loss, 4·1%).

2-Diethylaminoethyl p-*Glycylaminobenzoate Dihydrochloride.*—A solution of 2-diethylaminoethyl *p*-(phthalylglycylamino)benzoate monohydrate (3·8 g.) in ethanol (100 c.c.) was heated under reflux with aqueous hydrazine (33·2%, 0·9 c.c.) for 1 hr. Evaporation and treatment with 2N-hydrochloric acid precipitated phthalhydrazide which was removed after several hours at 0°. The gum left on evaporation of the filtrate was dissolved in ethanol and obtained solid by precipitation with ether. Crystallisation from ethanol–light petroleum (b. p. 60—80°) yielded *2-diethylaminoethyl* p-*glycylaminobenzoate dihydrochloride* as plates, m. p. 234° (decomp.) (Found: C, 49·0; H, 6·8; N, 11·1; Cl, 19·0. $C_{15}H_{23}O_3N_3$,2HCl requires C, 49·2; H, 6·9; N, 11·5; Cl, 19·4%).

Ethyl p-(*Phthalyl-*DL-*alanylamino*)*benzoate.*—Ethyl *p*-aminobenzoate (7·3 g., 2 mols.), dissolved in chloroform (30 c.c.), was stirred and slowly treated with a chloroform solution (30 c.c.) of phthalyl-DL-alanyl chloride (5·2 g., 1 mol.). When the solvent had been evaporated and the residue washed with 2N-hydrochloric acid, the product crystallised from ethanol as rods, m. p. 178°, consisting of *ethyl* p-(*phthalyl-*DL-*alanylamino*)*benzoate* (6·49 g., 80%) (Found: C, 65·5; H, 5·0; N, 7·4. $C_{20}H_{18}O_5N_2$ requires C, 65·6; H, 4·9; N, 7·6%).

Ethyl p-DL-*Alanylaminobenzoate Hydrochloride.*—Ethyl *p*-(phthalyl-DL-alanylamino)-benzoate (3·66 g.) in ethanol (100 c.c.) was heated with aqueous hydrazine solution (1 c.c., 33·2%) and the solution evaporated and freed from phthalhydrazide by treatment with 2N-hydrochloric acid in the usual way. The aqueous solution was evaporated and the product dried azeotropically, after which the *ethyl* p-DL-*alanylaminobenzoate hydrochloride* crystallised from *iso*propanol–light petroleum (b. p. 60—80°) as prisms (1·89 g., 69%), m. p. 224—225° (Found: C, 52·8; H, 6·4; N, 10·3. $C_{12}H_{16}O_3N_2$,HCl requires C, 52·8; H, 6·25; N, 10·3%).

2-Diethylaminoethyl p-(*Phthalyl-*DL-*alanylamino*)*benzoate.*—The material obtained from chloroform solutions of procaine and phthalyl-DL-alanyl chloride was soluble in alcohol and water but could not be crystallised. In aqueous solution with sodium picrate it gave *2-diethylaminoethyl* p-(*phthalyl-*DL-*alanylamino*)*benzoate picrate* which crystallised from moist ethanol in yellow needles, m. p. 203° (Found: C, 54·0; H, 4·7; N, 12·8. $C_{24}H_{27}O_5N_3$,$C_6H_3O_7N_3$ requires C, 54·1; H, 4·5; N, 12·6%).

Ethyl p-(*Phthalyl-γ-*DL-*glutamylamino*)*benzoate.*—A suspension of phthalyl-DL-glutamic anhydride (11·7 g.) in a solution of ethyl *p*-aminobenzoate (7·46 g.) in chloroform (120 c.c.) was stirred at room temperature. The anhydride gradually dissolved and when the nearly clear solution was filtered and set aside *ethyl* p-(*phthalyl-γ-*DL-*glutamylamino*)*benzoate* slowly separated.

It crystallised from aqueous ethanol in prisms (14·8 g., 77%), m. p. 189—190° (Found: C, 62·2; H, 4·4; N, 6·4. $C_{22}H_{20}O_7N_2$ requires C, 62·3; H, 4·7; N, 6·6%). When the mixture was heated under reflux solid material began to separate in 10 min. After further refluxing (total 1 hr.) the solution was set aside overnight at room temperature; the crystalline ester (93%), m. p. 187—188°, formed rectangular prisms, m. p. 189—190°, when recrystallised from aqueous ethanol.

p-(*Phthalyl-γ-*DL-*glutamylamino*)*benzoic Acid.*—*p*-Aminobenzoic acid (2·74 g.) and phthalyl-DL-glutamic anhydride (5·18 g.) were heated under reflux for 50 min. in dry dioxan (60 c.c.), and the solution was then evaporated. Hot water dissolved the gummy residue which later separated as a crystalline solid and formed nearly colourless prisms of p-(*phthalyl-γ-*DL-*glutamylamino*)*benzoic acid* (6·65 g., 84%), m. p. 237—238°, when crystallised from aqueous ethanol (Found: C, 60·3; H, 4·1; N, 7·3. $C_{20}H_{16}O_7N_2$ requires C, 60·6; H, 4·1; N, 7·1%). Recrystallisation (charcoal) raised the m. p. to 240—240·5°.

Ethyl p-(*γ-*DL-*Glutamylamino*)*benzoate.*—Ethyl *p*-(phthalyl-DL-glutamylamino)benzoate (12·72 g.) was dissolved in water (100 c.c.) containing sodium carbonate (3·48 g.) and treated with aqueous hydrazine (33·2%, 3 c.c.). The mixture was set aside at room temperature for three days, the solution becoming yellow and a white solid gradually separating. The solution was strongly acidified with hydrochloric acid and after an hour the phthalhydrazide was collected, the filtrate then being brought to pH 5·5 with aqueous sodium carbonate. The white precipitate of *ethyl* p-(*γ-*DL-*glutamylamino*)*benzoate* crystallised from aqueous ethanol in plates (6·0 g. 68%), m. p. 203·5° (Found: C, 57·2; H, 6·0; N, 9·3; carboxyl-N, 4·52. $C_{14}H_{18}O_5N_2$ requires C, 57·1; H, 6·2; N, 9·5; carboxyl-N, 4·76%). The ester gave a deep magenta colour with ninhydrin reagent.

DL-*Glutamic Acid γ-2-Phenyl*iso*propylamide.*—Powdered phthalyl-DL-glutamic anhydride (17·1 g.) slowly dissolved in a solution of amphetamine (8·9 g.) in pure dry chloroform (200 c.c.) with slight evolution of heat. The product failed to crystallise and it was therefore dissolved in water (250 c.c.) containing sodium carbonate (7·7 g.) and treated with aqueous hydrazine (6·6 c.c., 33·2%) during three days at room temperature. Acidification with hydrochloric acid (62·5 c.c.; 10N) and removal in due course of phthalhydrazide followed by the addition of sodium carbonate to pH 5·5 precipitated DL-*glutamic acid γ-2-phenyl*iso*propylamide* which crystallised from water as plates (10 g.), m. p. 216° (decomp.); the total yield with a further quantity (1·2 g.), m. p. 215—216° (decomp.), obtained by concentration of the mother-liquors, was 64% (Found: C, 63·9; H, 7·6; N, 10·7; carboxyl-N, 5·32. $C_{14}H_{20}O_3N_2$ requires C, 63·6; H, 7·6; N, 10·6; carboxyl-N, 5·30%). The pure compound gave a deep magenta colour with ninhydrin reagent.

THE UNIVERSITY, NOTTINGHAM [*Received, November 25th,* 1953.]

Syntheses from Phthalimido-acids. Part VI. Further Products from Phthalyl-*DL-*aspartic Anhydride, and the Preparation of Phthalyl-glycyl-*DL-*asparagine and -*DL-*serine.*

By F. E. KING, J. W. CLARK-LEWIS, and G. R. SMITH.

[Reprint Order No. 4833.]

Both α- and β-methyl esters are obtained from phthalyl-DL-aspartic anhydride and methanol. That which is formed in preponderating amount is the α-methyl compound since it is converted into an ester-amide identical with phthalylasparagine methyl ester.

Phthalylglycyl chloride, the azide, and the ethyl carbonic anhydride have each been used in the preparation of phthalylglycyl-asparagine and -DL-serine.

EXAMPLES described in earlier papers of this series (*J.*, 1949, 3315; 1951, 243; 1954, 1044) show that the action of amino-compounds and also of methanol and benzyl alcohol on phthalyl-DL- and -L-glutamic anhydride leads, at least qualitatively, to the formation of γ-derivatives. Only a limited investigation has so far been made of the reactions of

* Part V, preceding paper.

phthalyl-DL- and -L-aspartic anhydride, but as already recorded in Part III (*J.*, 1951, 2976) the ammonolysis of these two compounds yields β-amides, a result which is comparable with the behaviour of the corresponding phthalylglutamic anhydrides.

Included in the present communication on the preparation of new derivatives of DL-aspartic acid is an account of the action of methanol on phthalyl-DL-aspartic anhydride. A methanol solution of the anhydride afforded two products, (A) m. p. 182° (yield 57%), crystallising from the cold solution, and (B) m. p. 147—148° (yield 36%), which was obtained when the remaining liquid was concentrated. Both were acid esters and were converted through their acid chlorides into amido-esters, which were also formed from the corresponding azides and from the mixed carbonic anhydrides. The structures of the isomeric amido-esters were determined by esterifying, with diazomethane, the phthalyl-DL-asparagine prepared as in Part III (*loc. cit.*), whereupon a product was obtained identical with that originating from (A); this identified the compounds (A) and (B) as α- and β-methyl phthalyl-DL-aspartate respectively. The formation of two products, the α-isomer predominating, is thus in marked contrast to the conversion of the phthalylaspartic anhydride into phthalylasparagine and of the phthalylglutamic anhydride into γ-derivatives. Amides of the methyl ester (A) were prepared from *p*-aminobenzoic acid and its ethyl ester by the mixed carbonic anhydride synthesis.

Phthalylglycyl-DL-asparagine was prepared by coupling DL-asparagine with phthalylglycyl chloride in alkaline solution; treating the product with hydrazine gave glycyl-DL-asparagine, the racemic form of a component of the structure attributed by Woolley (*J. Biol. Chem.*, 1948, **176**, 1291) to lycomarasmin, *viz.*,

$$HO_2C{\cdot}CMe(OH){\cdot}NH{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CH(CO_2H){\cdot}CH_2{\cdot}CO{\cdot}NH_2.$$

Phthalylglycyl derivatives of serine and of its methyl ester which were synthesised in this way were also obtained from the azide and the ethyl carbonic anhydride of phthalylglycine.

Experimental

α-Methyl and β-Methyl Hydrogen Phthalyl-DL-aspartate.—A mixture of phthalyl-DL-aspartic anhydride (15 g.; Part III, *J.*, 1951, 2976) and dry methanol (150 c.c.) was boiled for 30 min. after dissolution was complete, and then kept at 0°. Crystallisation afforded *α-methyl hydrogen phthalyl-DL-aspartate* (9·9 g., 58%) as colourless prisms, m. p. 182° (Found: C, 56·1; H, 4·0; N, 4·91. $C_{13}H_{11}O_6N$ requires C, 56·3; H, 4·0; N, 5·1%).

The residue obtained by evaporating the filtrate from the α-ester was extracted with aqueous sodium hydrogen carbonate. Acidification of the extract (Congo-red) afforded *β-methyl hydrogen phthalyl-DL-aspartate* (6·1 g., 36%), m. p. 148—152°, as an oil which rapidly crystallised. The ester was very soluble in methanol; it crystallised from water in plates, m. p. 147—148° (Found: C, 56·3; H, 3·8; N, 5·0. $C_{13}H_{11}O_6N$ requires C, 56·3; H, 4·0; N, 5·1%).

Phthalyl-DL-asparagine Methyl Ester.—(*a*) Evaporation of the solution obtained by treating a suspension of phthalyl-DL-asparagine (1 g.; Part III, *loc. cit.*) in methanol (25 c.c.) with excess of ethereal diazomethane afforded a crystalline residue, which was washed with aqueous sodium hydrogen carbonate and with water. *Phthalyl-DL-asparagine methyl ester* crystallised from water in long rods, m. p. 170° (Found: C, 56·5; H, 4·4; N, 9·9. $C_{13}H_{12}O_5N_2$ requires C, 56·5; H, 4·4; N, 10·1%).

(*b*) α-Methyl hydrogen phthalyl-DL-aspartate was converted into the acid chloride (59%) with phosphorus pentachloride in ether, or more conveniently with thionyl chloride at the b. p. The acid chloride crystallised from light petroleum (b. p. 40—60°) in rosettes of needles, m. p. 77—78°. Addition of an excess of ethereal ammonia to the acid chloride (1 g.), in anhydrous ether, gave an immediate flocculent precipitate which was collected and washed with aqueous sodium hydrogen carbonate, and with water. Crystallisation from water afforded phthalyl-DL-asparagine methyl ester (0·82 g., 88%) in rods, m. p. 170°, not depressed by admixture with the amide described above.

(*c*) Addition of an excess of aqueous sodium azide (*ca.* 25%) to a concentrated acetone solution of the acid chloride [1 g.; prepared as in (*b*)] precipitated the α-methyl aspartate β-azide as an oil which rapidly crystallised. Extraction of the azide with ether and treatment with ethereal ammonia at 0° for 12 hr. afforded the amide (0·79 g., 85%), which crystallised from water in rods, m. p. and mixed m. p. 170°.

Phthalyl-DL-iso*asparagine Methyl Ester.*—(*a*) The acid chloride was obtained as an oil from β-methyl hydrogen phthalyl-DL-aspartate by the methods described above for the α-ester. When treated with ethereal ammonia the acid chloride afforded *phthalyl*-DL-iso*asparagine methyl ester* (50% from the acid) which crystallised from water in needles, m. p. 141° (Found: C, 56·4; H, 4·4; N, 10·1. $C_{13}H_{12}O_5N_2$ requires C, 56·5; H, 4·4; N, 10·1%).

(*b*) Addition of aqueous sodium azide (*ca.* 25%) to the foregoing acid chloride, in acetone, afforded the β-ester α-azide as an oil which, with ethereal ammonia at 0°, gave phthalyl-DL-*iso*asparagine methyl ester, m. p. 141°, identical with that obtained by method (*a*).

(*c*) A solution of β-methyl hydrogen phthalyl-DL-aspartate (1·4 g.) and triethylamine (0·7 c.c.) in dry dioxan (10 c.c.) was cooled to 10° and kept at this temperature for 10 min. after the addition of ethyl chloroformate (0·48 c.c.). The solution of the mixed anhydride was then treated with ethereal ammonia, and the flocculent amide was collected and washed with aqueous sodium hydrogen carbonate, and with water. Crystallisation of the residue (0·86 g., 61%) from water afforded phthalyl-DL-*iso*asparagine methyl ester in needles, m. p. 141° alone or when mixed with specimens prepared by methods (*a*) and (*b*).

Methyl β-(p-*Carboxyphenylcarbamyl*)-α-*phthalimidopropionate and its Ethyl Ester.*—A solution of the mixed anhydride, prepared from α-methyl hydrogen phthalyl-DL-aspartate (1·39 g.) and ethyl chloroformate as described under (*c*) above, was treated with a solution of *p*-aminobenzoic acid (0·69 g.) in N-sodium hydroxide (5 c.c.). Acidification (Congo-red) of the alkaline solution, after ether-extraction, with 5N-hydrochloric acid and storage at 0° afforded *methyl* β-(p-*carboxyphenylcarbamoyl*)-α-*phthalimidopropionate* (1·3 g., 66%), m. p. 260—262° (decomp.), raised to 264—265° (decomp.) by recrystallisation (plates) from aqueous ethanol or aqueous dioxan (Found: C, 61·1; H, 4·2; N, 7·4. $C_{19}H_{16}O_7N_2$ requires C, 60·6; H, 4·1; N, 7·1%).

In a similar manner the addition of a chloroform solution of ethyl *p*-aminobenzoate (0·83 g.) afforded the corresponding ethyl ester (1·84 g., 87%), which was isolated by evaporation of the solvents. *Methyl* β-(p-*ethoxycarbonylphenylcarbamoyl*)-α-*phthalimidopropionate* crystallised from aqueous 2-ethoxyethanol in plates, m. p. 205—207° (Found: C, 62·6; H, 4·5; N, 6·4. $C_{22}H_{20}O_7N_2$ requires C, 62·3; H, 4·7; N, 6·6%).

Phthalylglycyl-DL-*asparagine.*—Solutions of phthalylglycyl chloride (4·47 g.) in dioxan (15 c.c.) and of N-sodium hydroxide (20 c.c.) were added simultaneously during 1 hr. to a stirred solution of DL-asparagine (2·64 g.) in N-sodium hydroxide (20 c.c.) at 0°. The solution was acidified (litmus) and concentrated to small bulk under reduced pressure and stored at 0° after the addition of a little 2N-hydrochloric acid. Crystallisation of the precipitate afforded *phthalylglycyl*-DL-*asparagine* (2·6 g., 41%) in needles, m. p. 205—206° (decomp.), raised to 208—209° (decomp.) by recrystallisation from water (Found: C, 53·0; H, 4·2; N, 12·8. $C_{14}H_{13}O_6N_3$ requires C, 52·7; H, 4·1; N, 13·2%).

Glycyl-DL-*asparagine.*—A solution of phthalyl-DL-asparagine (3·19 g.) and sodium carbonate (0·58 g.) in water (60 c.c.) was treated with aqueous hydrazine (33%; 1 c.c.) at room temperature for 3 days, and then acidified (Congo-red) with hydriodic acid. After storing the solution at 0° phthalhydrazide was removed by filtration, the filtrate evaporated to dryness below 45°, and the residue was extracted with a small volume of water. Dilution of the extract with a large volume of ethanol precipitated *glycyl*-DL-*asparagine* (1·55 g., 82%), m. p. 204—206° (decomp.), raised by crystallisation from aqueous ethanol to 215—216° (decomp.), after discoloration at 210°. When heated rapidly it had m. p. 222° (decomp.), after discoloration at 216° (Found: C, 37·9; H, 6·2; N, 21·5. $C_6H_{11}O_4N_3$ requires C, 38·1; H, 5·9; N, 22·2%).

Phthalylglycyl-DL-*serine.*—(*a*) A solution of DL-serine (1·05 g.) and sodium hydrogen carbonate (1·85 g.) in water (20 c.c.) was cooled to 0° and stirred vigorously during the dropwise addition (1 hr.) of a solution of phthalylglycyl chloride (2·24 g.) in benzene (40 c.c.). After a further hour's stirring the aqueous phase was acidified with 5N-hydrochloric acid and storage at 0° for several hours gave a precipitate (1·8 g.), m. p. 193—195° (decomp.), which crystallised from water in small plates, m. p. 194° (decomp.). Extraction of this material with hot ethyl acetate and crystallisation from water afforded *phthalylglycyl*-DL-*serine monohydrate* (1·3 g., 42%) as plates, m. p. 199° (decomp.) (Found: C, 50·2; H, 4·8; N, 9·0; loss on drying *in vacuo*, 6·0. $C_{13}H_{12}O_6N_2,H_2O$ requires C, 50·3; H, 4·5; N, 9·0; loss, 5·8%). Emerson (U.S.P. 2,498,665; *Chem. Abs.*, 1950, **44**, 4926b) records m. p. 191° for phthalylglycyl-DL-serine prepared in a similar manner.

(*b*) Crystalline phthalylglycine azide from phthalylglycyl chloride (1·12 g.) was dissolved in dioxan and added to a solution of DL-serine (0·53 g., 1 equiv.) in N-sodium hydroxide (5 c.c.) at 0°, and a further 5 c.c. of N-sodium hydroxide was added after 2 hr. The mixture was kept at room temperature for 5 hr., extracted with ether, and acidified (Congo-red) with 5N-hydrochloric acid. Collection of the precipitate after storage at 0° for 12 hr. afforded phthalylglycyl-

DL-serine monohydrate (0·65 g., 42%), m. p. 192—193° (decomp.), raised to 199° (decomp.) by recrystallisation from water.

(*c*) A solution of DL-serine (0·53 g.) in N-sodium hydroxide was added to a solution of the mixed anhydride prepared in the usual way from phthalylglycine (1·03 g.) and ethyl chloroformate, at 10°. When gas evolution ceased the solution was extracted with ether and acidified (Congo-red) with 5N-hydrochloric acid. Crystallisation afforded phthalylglycyl-DL-serine monohydrate (0·94 g., 61%), m. p. 199° (decomp.) alone or mixed with the specimens prepared by methods (*a*) and (*b*).

Phthalylglycyl-DL-serine Methyl Ester.—(*a*) DL-Serine methyl ester hydrochloride, m. p. 135—136°, was prepared by the method of Fischer and Suzuki (*Ber.*, 1905, **38**, 4193) who give m. p. 114°. A chloroform solution of phthalylglycyl chloride (1 equiv.) was added during 1 hr. to a stirred solution of DL-serine methyl ester hydrochloride (1 equiv.) and triethylamine (2 equivs.) in chloroform. The residue obtained by evaporation of the solvent was washed with 2N-hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and with water; crystallisation from water afforded *phthalylglycyl-DL-serine methyl ester* (76%) as needles, m. p. 225° (decomp.) (Found: C, 54·8; H, 4·9; N, 9·1. $C_{14}H_{14}O_6N_2$ requires C, 54·9; H, 4·6; N, 9·2%).

(*b*) A chloroform solution of phthalylglycine azide (from 2·24 g. of phthalylglycyl chloride) was added to a solution of serine methyl ester hydrochloride (1·56 g., 1 equiv.) and triethylamine (1·38 c.c., 1 equiv.) in chloroform (20 c.c.) and kept at room temperature for 24 hr. Evaporation of the solvent left a residue which, after washing and crystallisation as described under (*a*), afforded phthalylglycyl-DL-serine methyl ester (1·6 g., 52%), m. p. 224° (decomp.) alone or mixed with the ester obtained by method (*a*).

(*c*) Addition of a chloroform solution of DL-serine methyl ester (1·19 g., 1 equiv.) to the mixed anhydride from phthalylglycine (2·05 g.), ethyl chloroformate (0·96 c.c.), and triethylamine (1·4 c.c.), and isolation as described above afforded phthalylglycyl-DL-serine methyl ester (1·9 g., 62%), m. p. 222° (decomp.), raised to 224—225° by recrystallisation from water.

The authors are indebted to Imperial Chemical Industries Limited for a grant for the purchase of amino-acids, and to Messrs. Gray Knight & Co. Ltd., London, E.13, for a gift of glutamic acid. The award of a maintenance allowance (to G. R. S.) from the Department of Industrial and Scientific Research is gratefully acknowledged.

THE UNIVERSITY, NOTTINGHAM. [*Received, November 25th*, 1953.]

---

*Polycyclic Systems. Part VI.** 8-meso-α-*Naphthanthr*-10-*one and* 2 : 3-8 : 9-*Dibenzoperylene.*

By E. A. BRAUDE, J. S. FAWCETT, and A. A. WEBB.

[Reprint Order No. 4766.]

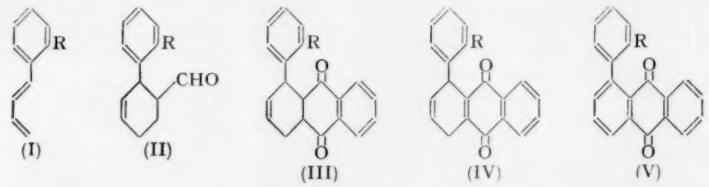
A novel route to certain types of condensed polycyclic benzenoid systems is illustrated by unambiguous syntheses of *meso*-α-naphthanthr-10-one and 2 : 3-8 : 9-dibenzoperylene *via* 1-*o*-tolyl- and 1 : 5-di-*o*-tolyl-anthraquinone.

The light absorption properties of these and related compounds are recorded and discussed.

IN two earlier papers (Braude and Fawcett, *J.*, 1951, 3113, 3117), a novel synthesis of phenanthridines and larger polycyclic systems embodying the phenanthridine skeleton was described which involves the cyclisation of Diels–Alder adducts of *o*-nitrophenylbutadiene (I; R = NO_2), with the nitro-group eventually furnishing the ring-nitrogen atom. An analogous route to phenanthrenes and larger polycyclic systems embodying the phenanthrene skeleton can be envisaged, which depends on the cyclisation of adducts of *o*-tolylbutadiene (I; R = Me) (Braude, Jones, and Stern, *J.*, 1947, 1087), with the *o*-methyl group eventually furnishing the 9-carbon atom. In the simplest case, the expected adduct (II; R = Me) of the diene with acraldehyde would be cyclised to give, after de-

* Part V, *J.*, 1953, 2208.

hydrogenation, phenanthrene itself. However, whereas phenylbutadiene (I; R = H) readily forms an adduct with acraldehyde (Lehmann and Paasche, *Ber.*, 1935, **68**, 1146; Lehmann, 1936, **69**, 631), no reaction could be induced with *o*-tolylbutadiene, even at 200°. Since *o*-nitrophenylbutadiene reacts even more readily than phenylbutadiene (Braude and Fawcett, *loc. cit.*), the inhibiting effect of the *o*-methyl group must be predominantly electronic rather than steric in origin and shows that Diels–Alder addition is retarded by electron-donating substituents in the diene.



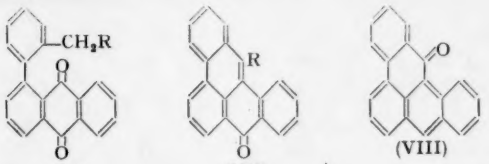
(I) (II) (III) (IV) (V)

Despite this discouraging result, the possibility of utilising the same approach in other cases of more direct interest was then investigated. In view of their greater reactivity, quinones represent a more suitable type of dienophile. Reaction of phenylbutadiene with naphtha-1 : 4-quinone in the absence of solvent or in hot nitrobenzene is accompanied by complete dehydrogenation, and gives 1-phenylanthraquinone (V; R = H) (Diels, Alder, and Stein, *Ber.*, 1929, **62**, 2337; Weizmann, Bergmann, and Haskelberg, *J.*, 1939, 391; Bergmann, Haskelberg, and Bergmann, *J. Org. Chem.*, 1942, **7**, 303). Reaction in ethanol at room temperature in the presence of a trace of quinol, however, gave mainly the 1 : 4-dihydro-derivative (IV; R = H), and in ethanol at 160—220° a mixture of the latter and the anthraquinone was obtained. *o*-Tolylbutadiene similarly gave 1 : 4-dihydro-1-*o*-tolylanthraquinone (IV; R = Me) and 1-*o*-tolylanthraquinone (V; R = Me) in about 50% total yield, and the dihydro-derivative was quantitatively converted into the fully dehydrogenated product by treatment with oxygen in alcoholic potassium hydroxide. The positions of the two extra hydrogen atoms in the dihydro-derivatives follow from the ultra-violet light absorption which resembles that of naphtha-1 : 4-quinone (see below). The 11 : 12-hydrogen atoms in the original adducts (III) are evidently even more labile than the 1 : 4-hydrogen atoms, in conformity with general experience (cf. Diels and Alder, *loc. cit.*; Fieser, *J. Amer. Chem. Soc.*, 1948, **70**, 3165; Braude and Fawcett, *loc. cit.*; *J.*, 1952, 1528).

The projected conversion of *o*-tolylanthraquinone into *meso*-α-naphthanthr-10-one (VII; R = H) is formally analogous to Scholl's classical synthesis (*Ber.*, 1910, **43**, 346) of pyranthrone dyes from 2 : 2′-dimethyl-1 : 1′-dianthraquinonyl. However, the methyl groups in the latter are exceptionally reactive and attempts to dehydrate *o*-tolylanthraquinone directly by the action of alkali at elevated temperatures yielded mainly unchanged starting material. Other methods of cyclisation were therefore sought and the following successful procedure was developed. Reaction of the quinone with one mol. of *N*-bromosuccinimide gave the *o*-bromomethyl derivative (VI; R = Br) the constitution of which was confirmed by hydrolysis to the hydroxymethyl derivative (VI; R = OH) and oxidation to the carboxylic acid (V; R = CO_2H). Ring-closure of the bromomethyl derivative was first attempted by conversion into the Grignard derivative and internal addition to the carbonyl group, but no reaction with magnesium or lithium could be induced. However, treatment with potassium cyanide in boiling aqueous dioxan resulted in a smooth replacement reaction accompanied by dehydration *in situ* of the resulting cyanomethyl derivative (VI; R = CN) to the cyano-*meso*-α-naphthanthrone (VII; R = CN). This step resembles the intramolecular condensation of benzyl cyanides with quinones in the Hinsberg synthesis of anthracenes (*Ber.*, 1910, **43**, 1360; cf. Moureu, Chovin, and Rivoal, *Bull. Soc. chim.*, 1946, **13**, 106; 1948, **15**, 99; Orchin and Reggel, *J. Amer. Chem. Soc.*, 1951, **73**, 436; Mosby, *ibid.*, 1953, **75**, 3600).

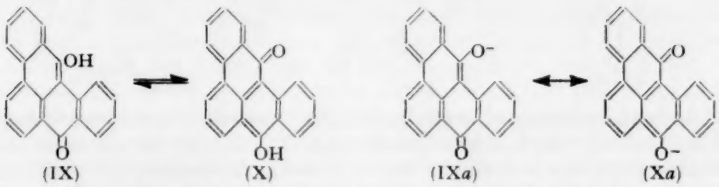
When heated with potassium hydroxide in ethylene glycol, the cyanide (VII; R = CN) underwent hydrolysis and decarboxylation to the naphthanthrone (VII; R = H). The

same constitution had previously been assigned by Clar (*Ber.*, **1943**, **76**, 609) to a product for which he reported somewhat different physical properties; he obtained it by a series of reactions which could equally have led to the isomeric anthrone (VIII). However, the original specimen, kindly supplied by Dr. Clar, after purification gave no melting-point depression on admixture with our material and a re-determination of the ultra-violet light absorption confirmed that the two substances are, in fact, identical.



(VI) (VII) (VIII)

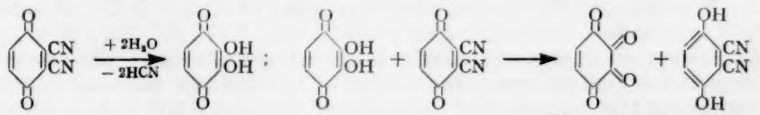
Hydrolysis of the cyanide (VII; R = CN) by concentrated sulphuric acid instead of alkali gave the very high-melting hydroxy-derivative (IX). Although nucleophilic substitution in reactive aromatic systems is well known (cf. Bunnett and Zahler, *Chem. Reviews*, 1951, **49**, 273), the replacement of —CN by —OH under *acid* conditions is somewhat unexpected; a good indication of the relatively high lability of cyano-substituents in quinonoid systems is, however, provided by the ready liberation of hydrogen cyanide from dicyanobenzoquinones (Thiele and Günther, *Annalen*, 1906, **349**, 51).* In the present case, attack by the hydrogen sulphate anion SO_4H^-, followed by hydrolysis, is presumably involved. The hydroxyanthrone can exist in two tautomeric forms (IX) and (X); its solutions in alkalis have a deep red colour due to the anion (IX*a*) ⟷ (X*a*) which is stabilised by charge-resonance.



(IX) (X) (IX*a*) (X*a*)

With a view to applying similar methods to the synthesis of larger polycyclic systems, the reactions of phenylbutadiene and *o*-tolylbutadiene with benzoquinone were next examined. When equimolar proportions of diene and quinone were used, only the mono-adducts (XI; R = H and Me) were formed (Braude, Jones, and Stern, *loc. cit.*) which were rearranged by acetic or stronger acid to the 5 : 8-dihydronaphthaquinols (XII).† The quinols are oxidised by nitrous acid to the 5 : 8-dihydronaphthaquinones (XIII) and by chromic acid to the naphthaquinones (XIV) (cf. Fieser, *loc. cit.*). It is of interest that 5 : 8-dihydro-1-*o*-tolylnaphthaquinone (XIII; R = Me) is stable to chromic acid and is evidently not an intermediate in the oxidation of (XII) to (XIV) (cf. Fieser, *loc. cit.*); this means that the dihydrobenzene ring in (XII) is oxidised before the quinol grouping.

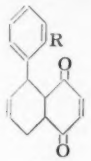
* The course of this interesting reaction, which also yields the corresponding dicyanoquinol, may be represented as follows:

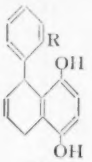


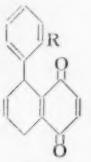
(Not isolated)

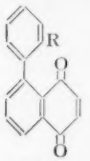
† The adduct (XI; R = H) has m. p. 101° (Braude, Jones, and Stern, *loc. cit.*). The compound, m. p. 170°, described by Weizmann, Bergmann, and Haskelberg (*loc. cit.*) as 5-phenyl-5 : 8 : 9 : 10-tetrahydronaphtha-1 : 4-quinone, is the quinol (XII; R = H) formed from the adduct under acidic conditions of isolation.

Further reaction of (XIII; R = Me) with *o*-tolylbutadiene in ethanol or nitrobenzene near 200° gave two products, a ditolylanthraquinone, m. p. 277°, and a tetrahydroditolylanthraquinone. The latter was oxidised, by passage of oxygen through its suspension in methanolic potassium hydroxide, to a second ditolylanthraquinone, m. p. 192°. Comparison with other pairs of 1 : 5- and 1 : 8-disubstituted anthraquinones suggested that the higher-melting ditolylanthraquinone is the 1 : 5- (XVIII; R = Me) and the lower-melting


(XI)

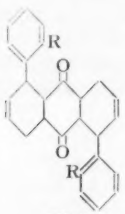

(XII)

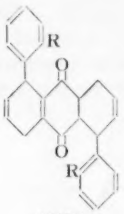

(XIII)

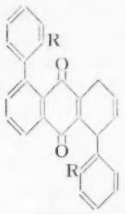

(XIV)

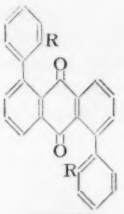
the 1 : 8-isomer (XXI; R = Me), and this assignment is confirmed by the reactions described later.

Since the yields of ditolylanthraquinones, particularly of (XVIII), obtained by stepwise addition were very low, the reaction of benzoquinone with two molar proportions of diene was studied. With phenylbutadiene in ethanol, the diadduct (XV; R = H) was


(XV)


(XVI)

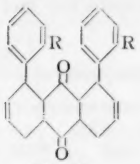

(XVII)

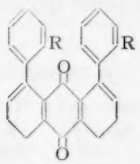

(XVIII)

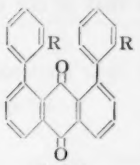
formed, while in the presence of acetic acid a 50% yield of a hexahydrodiphenylanthraquinone was obtained, which is formulated as (XVI; R = H) on the basis of its ultraviolet light absorption which resembles that of 5 : 8-dihydro-5-phenyl-1 : 4-naphthaquinone (Braude, Jones, and Stern, *J.*, 1947, 1087). In boiling ethanol and in boiling benzene, the yield of adduct (XV; R = H) is much reduced, and some dehydrogenation also occurs; the marked temperature effect suggests that the addition is reversible under these conditions. Oxidation of the adduct (XV; R = H), or its partial dehydrogenation products, with oxygen and alcoholic potassium hydroxide gave 1 : 5-diphenylanthraquinone (XVIII; R = H) previously prepared by Bergmann *et al.* (*loc. cit.*) by conducting the addition reaction in boiling nitrobenzene. The formulation of the quinone as (XVIII; R = H) rather than (XXI; R = H) is based on the high melting point, but, in contrast to several other cases (cf. Diels and Alder, *loc. cit.*; Braude and Fawcett, *loc. cit.*; and below), none of the 1 : 8-isomer was obtained.

The course of the diaddition of *o*-tolylbutadiene to benzoquinone proved to be remarkably sensitive to the experimental conditions. Depending on the solvent and temperature and on the presence of acids, oxidants or anti-oxidants, the 1 : 5- and 1 : 8-adducts (XV and XIX; R = Me), the two di-*o*-tolylanthraquinones (XVIII and XXI; R = Me), and a variety of intermediate dehydrogenation products (*e.g.*, XVII and XX; R = Me) were obtained; these products were separated by fractional crystallisation. The results do not fall into any well-defined pattern; thus, in ethanol 1 : 5-addition predominated at room temperature and at 170°, but only the 1 : 8-isomer was obtained at 80°, while in nitrobenzene at 100° the product varied from experiment to experiment. These irregularities probably arise from the reversibility of the addition reactions, coupled with a varying ease of dehydrogenation of the different adducts. It was found, however, that trichloroacetic acid which has been reported to catalyse Diels–Alder reactions (Wassermann, *J.*, 1942, 618, 623), and

methylene-blue which is a polymerisation inhibitor (Flaig, *Annalen*, 1950, **568**, 1), had a marked beneficial effect and by carrying out the reaction in the presence of these addenda in nitrobenzene, first at 150°, and then at 200°, 1 : 5-ditolylanthraquinone (XVIII; R = Me) was consistently obtained. The dehydrogenation mostly takes place at the higher temperature and the formation of water (from the reduction of nitrobenzene to aniline) can be clearly discerned. Even so, the yield of the anthraquinone is only 10%, much lower than with phenylbutadiene.


(XIX)

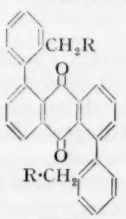

(XX)

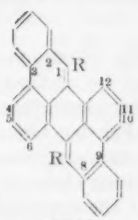

(XXI)

The double cyclisation of 1 : 5-di-*o*-tolylanthraquinone by a procedure analogous to that employed for 1-*o*-tolylanthraquinone presented no undue difficulty. Reaction with *N*-bromosuccinimide in the presence of benzoyl peroxide gave the dibromo-derivative (XXII; R = Br) which was converted by potassium cyanide in aqueous dioxan into the dicyanodibenzoperylene (XXIII; R = CN). Alkaline hydrolysis of the dicyanide at 180° afforded 2 : 3-8 : 9-dibenzoperylene (XXIII; R = H) in an overall yield of 25% based on ditolylanthraquinone. As would be expected, dibenzoperylene and its two derivatives are all high-melting substances which exhibit beautiful fluorescence in extremely dilute solutions.

It is interesting that 2 : 3-8 : 9-dibenzoperylene forms a sesquipicrate, whereas perylene forms a mono- and a di-picrate (Brass and Tengler, *Ber.*, 1931, **64**, 1650; Morgan and Mitchell, *J.*, 1935, 536). Adducts of this type containing fractional ratios of the two components appear to be rare, though a sesquistyphnate of pyrene has been reported by Shinomiya (*Bull. Chem. Soc. Japan*, 1940, **15**, 259; *Chem. Zentr.*, 1940, II, 3168).

Two dibenzoperylenes which could have the structure (XXIII; R = H) have previously been synthesized, one by the fusion of 9-bromophenanthrene with aluminium trichloride (Clar, *Ber.*, 1932, **65**, 846; Ioffé, *Trudvi Leningrad Khim. Technol. Inst.*, 1934, **1**, 116; *Chem. Abs.*, 1935, **29**, 7969) and the other by a similar fusion of 1 : 1′-diphenanthryl (Ioffé, *loc. cit.*) and 9 : 9′-diphenanthryl (Zinke, Ziegler, *et al.*, *Ber.*, 1941, **74**, 115; *Monatsh.*, 1951, **82**, 645). The two hydrocarbons have similar, though mutually depressed, melting points, and their structures have given rise to some controversy; the courses of the high-temperature fusion reactions are ambiguous and the differences between the spectral properties of the products are too small to allow of a definite assignment (Schauenstein


(XXII)


(XXIII)

(XXIV)

and Bürgermeister, *Ber.*, 1943, **76**, 205). Clar arbitrarily assumed his hydrocarbon to be 2 : 3-10 : 11-dibenzoperylene (XXIV), whereas subsequent workers favoured structure (XXIII; R = H). A comparison of the physical properties of the hydrocarbons with those of 2 : 3-8 : 9-dibenzoperylene obtained by the unambiguous synthesis now described, shows that Clar's product does, in fact, have this structure (XXIII; R = H).

Light Absorption Data.—The diene-quinone adducts (III), (XV), and (XIX) exhibit ultra-violet absorption due only to the isolated phenyl or substituted phenyl groups. Data

for the 1 : 4-dihydroanthraquinones and anthraquinones produced by dehydrogenation of the adducts are given in the Table, together with those previously obtained (Part II, *J.*, 1951, 3117; Part IV, *J.*, 1952, 1528) for the corresponding methoxy- and nitro-derivatives. The 1-aryl-1 : 4-dihydroanthraquinones (IV) absorb very similarly to naphthaquinone; there is little indication of significant interaction between the unconjugated aryl and the quinone chromophores in this system (cf. Braude, *J.*, 1949, 1902). Similarly, the absorption of 1-arylnaphthaquinones, and of 1-aryl- and 1 : 5- or 1 : 8-diarylanthraquinones, closely resembles that of the unsubstituted quinones, despite the fact that the aryl sub-

*Ultra-violet light absorption of aryl-substituted anthraquinone derivatives.**

1 : 4-*Naphthaquinones and* 1 : 4-*dihydroanthraquinones.*

	$\lambda_{max.}$ (Å)	ε	$\lambda_{max.}$ (Å)	ε	$\lambda_{max.}$ (Å) †	ε
Naphtha-1 : 4-quinone [1]	{ 2460 2560	19,000 13,500	3340	2750	4200	500
(XIV; R = Me) ‡	{ 2450 2520	22,000 21,000	3370	2500	4350	130
(IV; R = H)	2510	22,600	3320	4000	—	—
(IV; R = Me)	2500	20,000	3350	3600	—	—
(IV; R = OMe) [2]	{ 2590 2640	19,000 17,500	—	—	4130	1500
(XVII; R = Me)	{ 2570 2690	35,000 19,500	3380	3900	4130	220

Anthraquinones.

	$\lambda_{max.}$ (Å)	ε	$\lambda_{max.}$ (Å)	ε	$\lambda_{max.}$ (Å)	ε	$\lambda_{max.}$ (Å) †	ε
Anthraquinone [3]	2520	51,300	{ 2630 2720	20,400 20,400	3250	5600	4050	890
(V; R = H)	2510	44,500	—	—	3300	4250	—	—
(V; R = Me)	2560	50,000	2700	20,300	3310	5100	—	—
(V; R = OMe) [1]	{ 2440 2495	22,000 24,000	2670	19,000	3350	3300	—	—
(V; R = NO_2) [4]	2570	44,600	—	—	3380	2300	—	—
(XVIII; R = H)	{ 2510 2560	54,000	—	—	3410	6500	4150	430
(XVIII; R = Me)	2560	58,000	2700	25,600	3380	5700	4200	350
(XVIII; R = NO_2) [4]	{ 2510 2580	40,500 47,000	—	—	3300	7000	—	—
(XXI; R = Me)	2570	54,400	2710	26,000	3380	4500	—	—
(XXI; R = NO_2) [4]	2580	46,000	—	—	{ 3150 3300	8000 6300	—	—
(XXII; R = Br)	2570	53,000	—	—	3300	5500	4180	270

* Chloroform solutions. † In many cases, the long wave-length bands appear as shoulders rather than well-defined maxima. ‡ Ethanol solution.

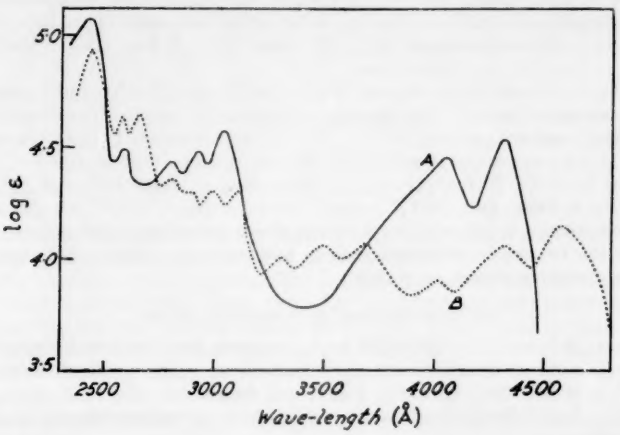
[1] Macbeth, Price, and Winzor, *J.*, 1935, 325 (in ethanol). [2] Braude and Fawcett, *J.*, 1952, 1528. [3] Morton and Earlam, *J.*, 1941, 159. [4] Braude and Fawcett, *J.*, 1951, 3117.

stituents are here attached directly to the chromophoric system. The absence of effective spectral interaction in this system must be ascribed to steric inhibition, similar to that observed in 1-phenylnaphthalene, 9-phenylanthracene and related examples (cf. Jones, *J. Amer. Chem. Soc.*, 1945, **67**, 2127; Friedel, Orchin, and Reggel, *ibid.*, 1948, **70**, 199), which opposes the adoption of a uniplanar arrangement by the two conjugated aryl groups. The behaviour of the arylanthraquinones may be contrasted with that of amino-, methoxy-, and nitro-anthraquinones which exhibit the expected substituent effects (Macbeth, Price, and Winzor, *J.*, 1935, 325; Morton and Earlam, *J.*, 1941, 159; Peters and Sumner, *J.*, 1953, 2101).

The light absorptions of the naphthanthrones (VII) resemble those of benzanthrone (cf. Clar, *Ber.*, 1932, **65**, 852) and the spectral properties of both the naphthanthrone and dibenzoperylene (see figure) are almost identical with those of some of their aza-analogues (Part II, *loc. cit.*). The fact that replacement of –CH= by –N= in aromatic systems has little effect on electronic spectra is well established (Braude, *Ann. Reports*, 1945, **42**, 108) and a similar correspondence has been observed in many other cases (cf. Barany,

Braude, and Pianka, *J.*, 1949, 1898; Albert, Brown, and Cheeseman, *J.*, 1951, 474; Clemo and Felton, *J.*, 1951, 671; Badger, Pearce, and Pettit, *J.*, 1951, 3199; Clemo and Mishra, *J.*, 1953, 192). Cyano substituents enhance the vibrational structure of the ultra-violet bands of both *meso*-naphthanthrone and dibenzoperylene, but the usually observed bathochromic effect is confined to the longest wave-length band of dibenzoperylene.

Light absorption of 2 : 3-8 : 9-*dibenzoperylene* (*A*) *and* 1 : 7-*dicyano*-2 : 3-8 : 9-*dibenzoperylene* (*B*) *in chloroform.*



Experimental

M. p.s marked K were determined on a Kofler block and are corrected. Analytical data were determined in the microanalytical laboratory of this Department (Mr. F. H. Oliver and staff). Light-absorption data, which are only given when not included in the Table, were determined by Mrs. I. A. Boston, using a photographic Hilger-Spekker instrument. Many of the substances described are highly fluorescent and the spectrographic technique employed was designed to minimise the effects of secondary emission (Braude, Fawcett, and Timmons, *J.*, 1950, 1019).

Addition reactions with phenylbutadiene.

1-*Phenylbuta*-1 : 3-*diene*.—This was prepared from cinnamaldehyde (Braude, Jones, and Stern, *J.*, 1947, 1087; Grummitt and Becker, *Org. Synth.*, 1950, **30**, 75) or, more conveniently, from crotonaldehyde. The freshly distilled aldehyde (88 g.) in ether (50 ml.) was added to a stirred solution of phenylmagnesium bromide (from Mg, 24 g., and bromobenzene, 159 g.) in ether (500 ml.) during 1 hr. at 0° (cf. Braude, Jones, and Stern, *J.*, 1946, 396). Stirring was continued for 2 hr. at room temperature and the solution was then cooled again to 0° and excess of saturated aqueous ammonium chloride was added. The ethereal layer was dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude 3-methyl-1-phenylallyl alcohol thus obtained was heated with anhydrous potassium hydrogen sulphate (10 g.) for 30 min. at 100°. The water formed was removed at 10 mm. and the product distilled, giving the diene (96 g., 74%), b. p. 67°/1 mm., n_D^{24} 1·6095, which solidified at 0° and then had m. p. 4°.

Addition to 1 : 4-*Naphthaquinone*.—(*a*) Diene (1 g.), naphthaquinone (1 g., prepared from naphthalene by the method of Braude and Fawcett, *J.*, 1951, 3117; *Org. Synth.*, 1953, **33**, 50), ethanol (5 ml.), and a trace of quinol were shaken for 4 days at room temperature. The product was filtered off, washed with cold methanol, and crystallised from ethanol, giving 1 : 4-*dihydro*-1-*phenylanthraquinone* (IV; R = H) (0·8 g.) as yellow needles, m. p. 139° (Found: C, 83·9; H, 5·0. $C_{20}H_{14}O_2$ requires C, 83·9; H, 4·9%).

(*b*) The diene (1 g.), the quinone (1 g.), ethanol (10 ml.), acetic acid (0·5 ml.), and a trace of quinol were heated for 12 hr. in a sealed tube at 200—220°. On cooling, 1-phenylanthraquinone (0·3 g.) was deposited which was filtered off and crystallised from ethyl acetate in yellow needles, m. p. 176° (Diels, Alder, and Stein, *Ber.*, 1929, **62**, 2337, give m. p. 177—178°). The filtrate, on being kept overnight, deposited 1 : 4-dihydro-1-phenylanthraquinone (0·65 g.), m. p. 139°.

Diaddition to 1 : 4-*Benzoquinone*.—(*a*) Diene (3 g.), quinone (1 g.), ethanol (10 ml.), and benzoyl peroxide (0·1 g.) were heated under reflux for 24 hr. On cooling, 1 : 4 : 5 : 8 : 11 : 12 : 13 : 14-octahydro-1 : 5-diphenylanthraquinone (XV; R = H) (0·3 g.) separated, which crystallised from ethyl acetate in fine colourless needles, m. p. 235° (Found : C, 84·4; H, 6·7. Calc. for $C_{26}H_{24}O_2$, C, 84·75; H, 6·6%) (Weizmann, Bergmann, and Haskelberg, *J.*, 1939, 396, give m. p. 230°). Light absorption in chloroform : $\lambda_{max.}$ 2580 Å, ε 980. The same product, though less pure, was obtained by refluxing the reactants in benzene for 1 hr., removing the solvent under reduced pressure, and adding ethanol.

The octahydroanthraquinone was suspended in a hot 1% solution of potassium hydroxide in ethanol, and oxygen was bubbled through it for a few minutes. This gave 1 : 5-diphenylanthraquinone, m. p. 345° (Bergmann *et al.*, *J.*, 1939, 391; *J. Org. Chem.*, 1942, **7**, 303, give m. p. 355°).

(*b*) Diene (2·4 g.), quinone (1 g.), ethanol (5 ml.), acetic acid (1 ml.), and quinol were shaken for 3 days at room temperature. The product which had separated was filtered off and crystallised from ethyl acetate, giving 1 : 4 : 5 : 8 : 11 : 12-*hexahydro*-1 : 5-*diphenylanthraquinone* (XVI; R = H) (1·1 g.) as very pale yellow needles, m. p. 185—186° (Found : C, 85·0; H, 6·1. $C_{26}H_{22}O_2$ requires C, 85·2; H, 6·05%). Light absorption in chloroform : $\lambda_{max.}$ 2690 (ε 5000), 2800 (ε 5000), 2910 (ε 3000), and 3630 Å (ε 200). Braude, Jones, and Stern (*loc. cit.*, 1947) give $\lambda_{max.}$ 2500 (ε 1450), 3640 Å (ε 53), etc., for 5 : 8-dihydro-5-phenylnaphthaquinone.

Oxidation of the hexahydroanthraquinone in hot ethanolic potassium hydroxide as above gave 1 : 5-diphenylanthraquinone, m. p. 345°.

Addition reactions with o-*tolylbutadiene.*

1-o-*Tolylbuta*-1 : 3-*diene*.—(*a*) This was best prepared from crotonaldehyde (1 mol.) and *o*-bromotoluene (1 mol.) as described for phenylbutadiene. The yield of diene, b. p. 82°/0·1 mm., n_D^{19} 1·5993, was 55—65% (Braude, Jones, and Stern, *loc. cit.*, 1947, give b. p. 37°/0·01 mm., n_D^{17} 1·6008). Rapid distillation and the addition of methylene-blue to inhibit polymerisation were advantageous.

(*b*) A warm solution of *o*-toluidine (214 g.) in 8M-hydrochloric acid was chilled and the fine crystalline suspension thus obtained was diazotised by addition of sodium nitrite (140 g.) in water (200 ml.) during 1·5 hr. at 0°. The resulting ice-cold solution was added during 2 hr. to a stirred mixture of butadiene (200 ml.), acetone (1·5 l.), water (300 ml.), sodium acetate (160 g.), and cupric chloride (60 g.) at −10°. Stirring was continued overnight at room temperature and the oily layer was then extracted with ether, washed with water, and dried (Na_2SO_4). Distillation gave 1-*chloro*-4-o-*tolylbut*-2-*ene* (213 g.), b. p. 72°/10^{-2} mm., n_D^{20} 1·5422 (Found : C, 73·8; H, 7·5; Cl, 18·0. $C_{11}H_{13}Cl$ requires C, 73·1; H, 7·2; Cl, 19·6%).

The chlorobutene (60 g.) was added to ethanol (1 l.) and potassium hydroxide (50 g.). No reaction occurred at room temperature. The solution was refluxed for 30 min. and then diluted with water and extracted with ether. Fractionation gave (i) *o*-tolylbutadiene (10 g.), b. p. 68°/1 mm., n_D^{16} 1·5960, and (ii) 1-*ethoxy*-4-o-*tolylbut*-2-*ene* (30 g.), b. p. 91°/1 mm., n_D^{18} 1·5250 (Found : C, 82·3; H, 9·3; OEt, 23·6. $C_{13}H_{18}O$ requires C, 82·1; H, 9·5; OEt, 23·7%).

(*c*) *o*-Bromomethyltoluene (148 g.; Atkinson and Thorpe, *J.*, 1907, **91**, 1695) in ether (300 ml.) was added to magnesium (20 g.) in ether (400 ml.), and the mixture stirred for 1 hr. Freshly distilled acraldehyde (45 g.) in ether (40 ml.) was added slowly at room temperature. After a further 2 hours' stirring excess of saturated aqueous ammonium chloride was added, the ethereal layer was separated and evaporated, and the viscous residue was distilled at 10^{-4} mm. 2 : 2′-Dimethyldibenzyl sublimed first and crystallised from pentane in colourless plates, m. p. 68° (Found : C, 91·3; H, 8·5. Calc. for $C_{16}H_{18}$: C, 91·4; H, 8·6%) (Baker, Banks, Lyon, and Mann, *J.*, 1945, 27, give m. p. 66·5°). This was followed by a small quantity of 1-*o*-tolylbut-3-en-2-ol which was dehydrated to 1-*o*-tolylbutadiene by distillation from potassium hydrogen sulphate.

Addition to Naphthaquinone.—(*a*) Diene (4 g.), quinone (3 g.), ethanol (20 ml.), and a trace of quinol were shaken for 48 hr. at room temperature. The dark blue product was filtered off and boiled with methanol. Recrystallisation from ethyl acetate gave 1 : 4-*dihydro*-1-o-*tolylanthra*-9 : 10-*quinone* (IV; R = Me) (3·7 g.) as yellow needles, m. p. 162° (Found : C, 84·0; H, 5·5. $C_{21}H_{16}O_2$ requires C, 84·0; H, 5·4%).

The dihydroquinone (1 g.) was suspended in hot 10% ethanolic potassium hydroxide, and oxygen was bubbled through the mixture for a few minutes. On dilution with water, 1-o-*tolylanthra*-9 : 10-*quinone* (V; R = Me) (0·9 g.) separated, which crystallised from ethanol in fine yellow needles, m. p. 149° (Found : C, 84·3; H, 4·8. $C_{21}H_{14}O_2$ requires C, 84·5; H, 4·7%).

(*b*) Diene (4 g.), quinone (3 g.), ethanol (20 ml.), and acetic acid (0·5 ml.) were heated in a sealed tube for 14 hr. at 180°. A small quantity of an insoluble green product was filtered off which, after crystallisation from nitrobenzene, had m. p. 380—390° (Found: C, 78·6; H, 3·0. Calc. for $C_{30}H_{14}O_5$: C, 79·3; H, 3·1%) and appears to be identical with a self-condensation product of naphthaquinone previously isolated by Pummerer and his co-workers (*Ber.*, 1937, **70**, 2281; 1938, **71**, 2569; 1939, **72**, 1623) and formulated by them as the anhydroquinhydrone of triphthaloylbenzene. The cooled solution slowly deposited 1-*o*-tolylanthraquinone (1·5 g.), m. p. 149°, and, after partial evaporation, 1 : 4-dihydro-1-*o*-tolylanthraquinone (1·6 g.), m. p. 162°, undepressed on admixture with the specimens obtained as under (*a*).

Monoaddition to Benzoquinone.—(*a*) Diene (6 g.), quinone (4 g.), and benzene (20 ml.) were refluxed for 30 min. Partial evaporation gave 5 : 8 : 9 : 10-tetrahydro-5-*o*-tolylnaphthaquinone (5 g.) which crystallised from light petroleum (b. p. 80—100°) in pale yellow plates, m. p. 93° (Braude, Jones, and Stern, *loc. cit.*, 1947, give m. p. 93—95°).

The tetrahydroquinone (2 g.) was dissolved in acetic acid (20 ml.) at 100°. Sodium nitrite (2 g.) in water (3 g.) was added to the hot solution. On cooling and dilution with water (10 ml.), 5 : 8-*dihydro*-5-o-*tolylnaphtha*-1 : 4-*quinone* (XIII; R = Me) (1·8 g.) separated, which crystallised from ethanol in yellow prisms, m. p. 123—124° (Found: C, 81·3; H, 5·7. $C_{17}H_{14}O_2$ requires C, 81·6; H, 5·6%).

The dihydronaphthaquinone was recovered unchanged after treatment with sodium dichromate in sulphuric and acetic acid for ½ hr. at 60° or 100°.

(*b*) Diene (4 g.), quinone (6 g.), benzene (20 ml.), trichloroacetic acid (50 mg.), and methylene-blue (10 mg.) were heated under reflux for 2 hr. The benzene was removed under reduced pressure and the residue was washed with a little ether, boiled with methanol, alumina, and charcoal, and then crystallised from aqueous methanol, giving 5 : 8-*dihydro*-5-o-*tolylnaphtha*-1 : 4-*quinol* (XII; R = Me) (4 g.), m. p. 168° (Found: C, 80·8; H, 6·6. $C_{17}H_{16}O_2$ requires C, 80·9; H, 6·4%).

To the dihydronaphthaquinol (2 g.) in acetic acid (20 ml.), sodium dichromate (2 g.) in 4N-sulphuric acid (5 ml.) was added slowly and the mixture then kept at 100° for 20 min. and finally cooled. Water was added and the product which separated was crystallised from aqueous methanol, giving 5-o-*tolylnaphtha*-1 : 4-*quinone* (XIV; R = Me) as yellow needles, m. p. 114—115° (Found: C, 82·0; H, 4·9. $C_{17}H_{12}O_2$ requires C, 82·2; H, 4·9%).

Addition to 5 : 8-*Dihydro*-5-o-*tolylnaphthaquinone.*—Diene (1 g.), quinone (1 g.), and ethanol (10 ml.) were heated in a sealed tube at 200° for 18 hr. On cooling, 1 : 5-di-*o*-tolylanthraquinone (0·15 g.), m. p. 278° (K), and 1 : 4 : 5 : 8-tetrahydro-1 : 8-di-*o*-tolylanthraquinone (0·1 g.), m. p. 218°, separated. Both m. p.s were undepressed on admixture with the authentic specimens described below.

A similar result was obtained by reaction in nitrobenzene at 190° for 1 hr.

Diaddition to Benzoquinone.—(*a*) Diene (2·8 g.), quinone (0·75 g.), and ethanol were shaken for 4 days at room temperature. The product was filtered off, washed with a little ethanol, and crystallised from ethyl acetate, giving 1 : 4 : 5 : 8 : 9 : 10 : 11 : 12-*octahydro*-1 : 5-*di*-o-*tolylanthra*-9 : 10-*quinone* (XV; R = Me) (0·3 g.) as colourless, hexagonal plates, m. p. 221—223° (Found: C, 84·7; H, 7·3. $C_{28}H_{28}O_2$ requires C, 84·8; H, 7·1%). Light absorption in chloroform: $\lambda_{max.}$ 2640 Å; ε 550. The same product in similar yield was usually obtained in the presence of a little acetic acid or quinol, but in one experiment, in the presence of quinol, 1 : 4 : 5 : 8-tetrahydro-1 : 8-di-*o*-tolylanthraquinone (see below, *b*), m. p. 219°, was isolated instead.

The octahydroanthraquinone (0·20 g.) was suspended in a boiling solution of potassium hydroxide (1 g.) in ethanol (10 ml.), and a rapid stream of oxygen was passed through the whole for 10 min. On cooling and dilution with water, 1 : 5-*di*-o-*tolylanthra*-9 : 10-*quinone* (XVIII; R = Me) (0·18 g.) separated, which was sublimed at 10^{-4} mm. and formed yellow plates, m. p. 278° (K) (Found: C, 86·8; H, 5·4. $C_{28}H_{20}O_2$ requires C, 86·6; H, 5·2%).

(*b*) Diene (2·8 g.), quinone (1 g.), and ethanol (5 ml.) were refluxed for 4 hr. On cooling, 3 : 4 : 5 : 6(?)-*tetrahydro*-1 : 8-*di*-o-*tolylanthra*-9 : 10-*quinone* (XX; R = Me) (0·3 g.) separated, which crystallised from ethyl acetate in orange needles, m. p. 219—221° (Found: C, 85·7; H, 6·4. $C_{28}H_{24}O_2$ requires C, 85·7; H, 6·2%). Light absorption in chloroform; $\lambda_{max.}$ 2650 (ε 10,000) and 3040 Å (ε 3600).

Oxidation of the tetrahydroanthraquinone (0·20 g.) in ethanolic potassium hydroxide as under (*a*) gave 1 : 8-*di*-o-*tolylanthra*-9 : 10-*quinone* (XXI; R = Me) (0·19 g.), which after sublimation formed yellow plates, m. p. 192° (Found: C, 86·1; H, 5·3. $C_{28}H_{20}O_2$ requires C, 86·6; H, 5·2%).

(*c*) Diene (2·8 g.), quinone (1 g.), and ethanol (10 ml.) were heated in a sealed tube at 170°

for 18 hr. The product was oxidised as above, giving 1 : 5-di-*o*-tolylanthraquinone (0·3 g.), m. p. 278° (K).

(*d*) Diene (4 g.), quinone (1 g.), nitrobenzene (10 ml.), and methylene-blue (5 mg.) were kept at 90° for 20 hr. and then refluxed for 10 min. The solvent was removed at 100°/1 mm. and the residue refluxed with a little ethanol for a few minutes. The crystalline, yellow product was recrystallised from xylene, giving 1 : 5-di-*o*-tolylanthraquinone (0·3 g.), m. p. 278°.

The same result was obtained on heating the mixture at 135° for 45 hr., but in one experiment in which acetic acid (2 ml.) was added, only tetrahydro-1 : 8-di-*o*-tolylanthraquinone (0·2 g.), m. p. 219°, was isolated after 18 hr. at 90°.

(*e*) Diene (3·4 g.), quinone (1 g.), nitrobenzene (10 ml.), and a trace of quinol were heated under reflux for 10 min. and then kept at 100° for 4 hr. Most of the nitrobenzene was removed at 100°/1 mm. and the residue diluted with ethanol. The product which separated is formulated as 1 : 4-*dihydro*-1 : 5-*di*-*o*-*tolylanthra*-9 : 10-*quinone* (XVII; R = Me) and sublimed in *vacuo*, giving fine yellow needles, m. p. 258° (Found: C, 86·1; H, 5·8. $C_{28}H_{22}O_2$ requires C, 86·1; H, 5·7%).

(*f*) Diene (10 g.), quinone (3 g.), nitrobenzene (50 ml.), trichloroacetic acid (0·5 g.), and methylene-blue (100 mg.) were heated to 150° in an oil-bath. Additional small portions of methylene-blue were added from time to time when the green colour of the solution began to change to brown. After 3 hr. at 150°, the temperature was raised to 200° for 1 hr. Working-up as under (*d*) and crystallisation from xylene–nitrobenzene containing a few drops of concentrated hydrochloric acid gave 1 : 5-di-*o*-tolylanthraquinone (1·0 g.), m. p. 277°. This is the most satisfactory procedure for the preparation of this compound and gave consistent results in several experiments.

meso-α-*Naphthanthrone* [*naphtha*(1′ : 2′ : 3′-1 : 13 : 9)*anthrone*].

Attempted Direct Cyclisation of 1-o-*Tolylanthraquinone*.—The quinone (2 g.), ethanol (15 ml.), and potassium hydroxide were heated in a sealed tube at 150° for 12 hr. On dilution with water, only unchanged quinone was recovered. The same result was obtained at 200°, with ethylene glycol as solvent.

1-o-*Bromomethylphenylanthra*-9 : 10-*quinone* (VI; R = Br).—1-*o*-Tolylanthraquinone (2 g.), *N*-bromosuccinimide (1·3 g.), carbon tetrachloride (20 ml.), and benzoyl peroxide (10 mg.) were heated under reflux for 12 hr. After filtration, the solution was diluted with methanol. The 1-o-*bromomethylphenylanthra*-9 : 10-*quinone* (2·2 g.) which separated crystallised from ethyl acetate as yellow plates, m. p. 181—182° (Found: C, 67·2; H, 3·8; Br, 21·1. $C_{21}H_{13}O_2Br$ requires C, 66·9; H, 3·5; Br, 21·2%). Light absorption in chloroform: $\lambda_{max.}$ 2520 (ε 51,000), 2560 (ε 56,000), 2730 (ε 21,500), and 3300 Å (ε 6300), $\lambda_{infl.}$ 2780 Å (ε 20,000).

No reaction occurred between the bromide and various forms of " activated " magnesium, or with lithium, in boiling ether–benzene, and unchanged bromide was recovered.

1-o-*Hydroxymethylphenylanthra*-9 : 10-*quinone* (VI; R = OH).—The foregoing bromide (0·35 g.), potassium carbonate (0·1 g.), dioxan (36 ml.), and water (4 ml.) were heated under reflux for 24 hr. Dilution with water, extraction with benzene, and evaporation gave 1-o-*hydroxymethylphenylanthra*-9 : 10-*quinone* (0·25 g.) which separated from light petroleum (b. p. 60—80°) in yellow crystals, m. p. 153° (Found: C, 79·5; H, 4·2. $C_{21}H_{14}O_3$ requires C, 80·2; H, 4·5%). Light absorption in chloroform: $\lambda_{max.}$ 2560 (ε 51,000), 2730 (ε 20,500), and 3320 Å (ε 5300).

1-o-*Carboxyphenylanthra*-9 : 10-*quinone* (V; R = CO_2H).—The foregoing hydroxymethyl compound (0·24 g.) in acetone (5 ml.) was oxidised by the addition of potassium permanganate (0·5 g.) in aqueous sodium carbonate (8 ml.). The mixture was stirred for 30 min., then filtered and acidified with hydrochloric acid. The precipitated *acid* (0·15 g.) crystallised from ethanol in yellow needles, m. p. 212° (Found: C, 77·3; H, 4·0. $C_{21}H_{12}O_4$ requires C, 76·8; H, 3·7%).

4′-*Cyanonaphtha*(1′ : 2′ : 3′-1 : 13 : 9)*anthrone* (VII; R = CN).—1-*o*-Bromomethylphenylanthraquinone (2 g.), potassium cyanide (0·6 g.), dioxan (180 ml.), and water (20 ml.) were heated under reflux for 18 hr. On cooling and addition of water (50 ml.) the *cyanonaphthanthrone* (1·6 g.) separated, which crystallised from dioxan in fine yellow needles, m. p. 261—262° (Found: C, 86·7; H, 3·7; N, 4·4. $C_{22}H_{11}ON$ requires C, 86·6; H, 3·6; N, 4·6%). Light absorption in chloroform: $\lambda_{max.}$ 2440 (ε 49,000), 2510 (ε 47,000), 2670 (ε 30,500), and 3900 Å (ε 20,000); $\lambda_{infl.}$ 2930 (ε 12,000), 3080 (ε 10,500), and 3160 Å (ε 10,000).

meso-α-*Naphthanthrone* (VII; R = H).—The foregoing cyano-derivative (1 g.), ethylene glycol (5 ml.), and potassium hydroxide (2 g.) were kept at 160° in a copper flask for 4 hr., then cooled. 50% Sulphuric acid (20 ml.) was slowly added and the precipitate was filtered off, washed, and dried. Crystallisation from dioxan gave the naphthanthrone (0·8 g.) as yellow needles,

m. p. 232°, 240° (K) (Found: C, 89·9; H, 4·4. Calc. for $C_{21}H_{12}O$: C, 90·0; H, 4·3%). The sample described (*Ber.*, 1943, **76**, 609) and kindly supplied by Dr. Clar had m. p. 226°, 237° (K), mixed m. p. 226°. Both samples showed identical light absorption in ethanol: $\lambda_{max.}$ 2410 (ε 53,000), 2650 (ε 28,000), 3020 (ε 22,500), and 3950 Å (ε 14,500); $\lambda_{infl.}$ 2890 (ε 20,500) and 3120 Å (ε 17,500) (for full curve, see Braude and Fawcett, *J.*, 1951, 3119) (Clar, *loc. cit.*, gives $\lambda_{max.}$ 2410, 2700, 2900, 3030, 3180, and 4040 Å).

4′-*Hydroxynaphtha*(1′ : 2′ : 3′-1 : 13 : 9)*anthrone* (VII; R = OH).—The above cyano-derivative (1 g.) and concentrated sulphuric acid (10 ml.) were heated to 170° for 4 hr. The mixture was poured on ice and made alkaline with aqueous sodium hydroxide. The resulting deep-red solution was filtered and acidified with sulphuric acid. The flocculent, yellow precipitate was filtered off, washed, dried, and sublimed at 280° in *vacuo*, giving fine yellow needles of the 4′-*hydroxy-ketone* (0·25 g.) (Found: C, 85·6; H, 4·3. $C_{21}H_{12}O_2$ requires C, 85·1; H, 4·1%). It had no definite m. p. and was practically insoluble in common organic solvents.

2 : 3-8 : 9-*Dibenzoperylene*.

1 : 5-*Di*-(o-*bromomethylphenyl*)*anthra*-9 : 10-*quinone* (XXII; R = Br).—1 : 5-Di-*o*-tolylanthraquinone (1·16 g.), *N*-bromosuccinimide (1·60 g., freshly crystallised and dried; cf. Chapman and Williams, *J.*, 1952, 5044; Kooyman, Helden, and Bickel, *Proc. K. Ned. Akad. Wet.*, 1953, *B*, **56**, 75), carbon tetrachloride (25 ml.), chloroform (5 ml.), and benzoyl peroxide (40 mg.) were heated under reflux with exclusion of moisture. The solution became first deep-red and later light yellow. After 6 hr. succinimide (0·76 g., 84%), m. p. 126—128°, was filtered off and the solvent removed under reduced pressure, leaving the *dibromo*-derivative (1·05 g.). Recrystallised from benzene–light petroleum (b. p. 60—80°) it formed yellow needles, m. p. 184—187° (Found: Br, 30·4. $C_{28}H_{18}O_2Br_2$ requires Br, 29·3%).

1 : 7-*Dicyano*-2 : 3-8 : 9-*dibenzoperylene* (XXIII; R = CN).—The foregoing crude dibromo-derivative was dissolved in dioxan (45 ml.), and potassium cyanide (1·5 g.) in water (5 ml.) was added. The clear solution was then heated under gentle reflux for 12 hr. The solvents were removed under reduced pressure and the residue was washed with water. A portion of the crude *dicyanodibenzoperylene* (0·9 g.) thus obtained was crystallised from nitrobenzene, giving orange needles, m. p. >360° (Found: N, 6·3. $C_{30}H_{14}N_2$ requires N, 7·0%). Light absorption in chloroform: $\lambda_{max.}$ 2430 (ε 84,000), 2560 (ε 44,000), 2650 (ε 44,000), 2800 (ε 23,000), 2980 (ε 20,000), 3100 (ε 20,000), 3300 (ε 10,000), 3480 (ε 12,000), 3670 (ε 12,000)· 4020 (ε 8000), 4330 (ε 12,000), and 4560 Å (ε 14,000) (see also curve, p. 1055). Dilute solutions of the dinitrile in chloroform, dioxan, or nitrobenzene were yellow-green and exhibited an intense green fluorescence.

2 : 3-8 : 9-*Dibenzoperylene* (XXIII; R = H).—The foregoing crude dinitrile, ethylene glycol (10 ml.), and potassium hydroxide (3·0 g.) were heated under reflux for 6 hr., during which the colour of the solution changed from intense green to deep-red. The solution was acidified with 50% sulphuric acid, and the yellow-brown precipitate was extracted with boiling methanol in a modified Soxhlet apparatus. On acidification of the red, bright pink-fluorescent methanol solution with sulphuric acid, an amorphous brown product was precipitated.

The methanol-insoluble product was extracted with boiling xylene. The deep-red, green-fluorescent solution was boiled with charcoal, filtered, and concentrated. Addition of ether to the cooled concentrate precipitated golden spangles of the dibenzoperylene (0·25 g.), m. p. 339—342°. Crystallisation from xylene–nitrobenzene gave golden-yellow plates, m. p. 342° (Found: C, 94·8; H, 4·7. $C_{28}H_{16}$ requires C, 95·4; H, 4·6%) (Clar, *Ber.*, 1932, **65**, 846, gives m. p. 343°). Light absorption in chloroform: $\lambda_{max.}$ 2420 (ε 116,000), 2560 (ε 31,000), 2800 (ε 27,000), 2910 (ε 31,000), 3020 (ε 39,000), 4050 (ε 27,000), and 4300 Å (ε 35,000) (see also curve, p. 1055) (Clar, *loc. cit.*, gives $\lambda_{max.}$ 2900, 3020, 3850, 4050, and 4300 Å, log ε 4·6, 4·7, 4·3, 4·6, and 4·6 respectively). Dibenzoperylene is very sparingly soluble in boiling benzene, ether, chloroform, etc., giving orange solutions with a blue fluorescence. Solutions in nitrobenzene are deep red with a blue fluorescence. With concentrated sulphuric acid in the cold, the hydrocarbon gives a green colour changing rapidly to bright purple. It formed a *picrate* which crystallised from xylene in plates, m. p. 239—242° (Found: C, 63·3; H, 3·4; N, 8·6. $2C_{28}H_{16}.3C_6H_3O_7N_3$ requires C, 63·8; H, 3·0; N, 9·05%) (Clar, *loc. cit.*, gives m. p. 240°, but no analytical data).

The provision of grants by the Department of Scientific and Industrial Research (to J. S. F.) and the Ministry of Education (to A. A. W.) is gratefully acknowledged.

Department of Organic Chemistry, Imperial College of Science and Technology, South Kensington, London, S.W.7. [*Received, November 3rd*, 1953.]

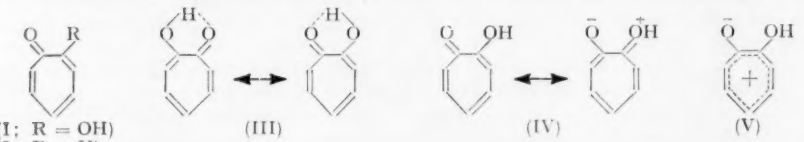
Tropolones. Part VIII. Synthesis and Properties of 7-Hydroxybenzocycloheptatrien-3-one.*

By G. L. Buchanan.

[Reprint Order No. 4793.]

The bicyclic compound (X), named in the title, has been synthesised from benzo*cyclo*heptene-3 : 7-dione (VI), and its properties compared with those of αβ-benzotropolone.

Considerations of fine structure have led to two conflicting views on the aromaticity of tropolone (I). The first was advanced by Dewar (*Nature*, 1945, **155**, 50), who originally postulated hydrogen-bonded structures (III) as the principal resonance forms, but later (*idem*, *ibid.*, p. 479) modified this in favour of the ionic resonance structures (IV). Koch (*J.*, 1951, 512) subscribed to this latter view on the basis of infra-red studies, and postulated simple prototropy to account for the symmetry of the molecule. These views agree in implicating both oxygen atoms in the fundamental resonance of the molecule. They are, however, open to the criticism (Cook and Loudon, *Quart. Reviews*, 1951, **5**, 99) that the bond between the oxygen-bearing carbon atoms is always represented as a single bond, whereas, lack of double-bond character is not substantiated by bond-length measurements (Robertson, *J.*, 1951, 1222). A second view, relating tropolone to *cyclo*heptatrienone (II), suggests that the latter is the parent substance of this new aromatic system (Buchanan, *Chem. and Ind.*, 1952, 855; Doering and Knox, *J. Amer. Chem. Soc.*, 1952, **74**, 5683). This implies major contributions from structures (V) in agreement with Nozoe's opinion (*Proc. Japan Acad.*, 1950, **26**, 30), and seems more satisfactory since it demands a regular heptagon



(I; R = OH)
(II; R = H)

(III) (IV) (V)

structure, in agreement with *X*-ray data (Robertson, *loc. cit.*). It implies, however, that the second oxygen atom is not involved in the fundamental resonance of the molecule, and hence, that its position in the ring may be varied without affecting the fundamental character of the ring. It is therefore of interest to examine the properties of isomeric structures (*i.e. iso*tropolones) in which the oxygen atoms are not vicinal. The present communication describes the preparation and properties of 7-hydroxybenzo*cyclo*heptatrien-3-one (X), an isomer of αβ-benzotropolone (XII).

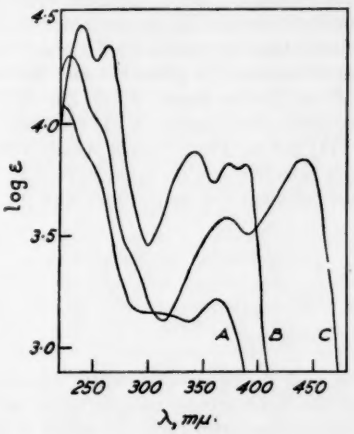
Preparation of the hydroxy-ketone (X) was attempted initially by the methods used in the preparation of the tropolone (XII) (Cook and Somerville, *Nature*, 1949, **163**, 410; Cook, Gibb, Raphael, and Somerville, *J.*, 1952, 603). Dehydrogenation of the dione (VI) by means of palladium–charcoal, however, failed to give an acidic product, and bromination by bromine in glacial acetic acid followed by alkali treatment yielded only dark oils. A much cleaner reaction took place with *N*-bromosuccinimide, and the bromo-derivative was readily dehydrobrominated by aqueous trimethylamine, affording a product, $C_{11}H_8O_2$, which gave a bis-2 : 4-dinitrophenylhydrazone but no picrate. It was insoluble in aqueous alkali, stable towards cold aqueous potassium permanganate, and failed to give a colour with ferric chloride. Such properties are incompatible with structure (X) (see below), and the compound is provisionally assigned the formula (VII).

To avoid ring formation during the dehydrogenation of the diketone (VI) the latter was converted by means of *iso*propenyl acetate (Hagemeyer and Hull, *Ind. Eng. Chem.*, 1949, **41**, 2920) into the bis-enol acetate (VIII), which was brominated by means of *N*-bromosuccinimide. This type of reaction produces αβ-unsaturated ketones (Gallacher, *J. Org.*

* Part VII, *J.*, 1954, 530.

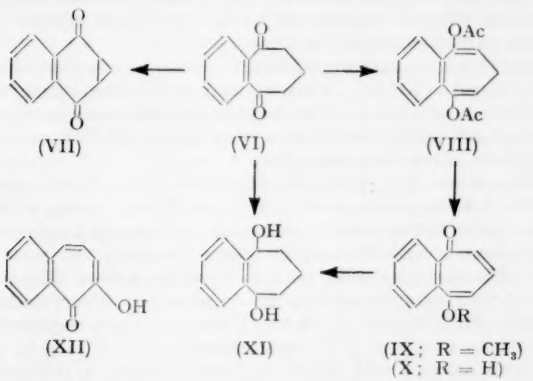
Chem., 1949, **14**, 660), and the neutral oily product obtained here is presumably the acetate of (X). Alkaline hydrolysis followed by acidification gave 7-hydroxybenzo*cyclo*heptatrien-3-one (X) as a yellow solid, readily subliming *in vacuo*. It behaves as an acid (pK 6·40), dissolves with effervescence in sodium hydrogen carbonate solution, and rapidly decolorizes aqueous potassium permanganate. Its structure was confirmed by its reduction to the diol (XI), which can also be prepared from the diketone (VI).

The *iso*tropolone (X) resembles αβ-benzotropolone (XII) in some respects. It gives a 3 : 5-dinitrobenzoate, an oily acetate, a yellow picrate, a red-brown colour with ferric chloride, and it couples with diazotised aniline, giving a crimson dye. It also forms unstable salts with hydrochloric and perchloric acids, but in contrast to (XII) it forms a 2 : 4-dinitrophenylhydrazone, is almost insoluble in non-polar solvents, fails to form a copper



A, 7-*Methoxybenzo*cyclo*heptatrien*-3-*one* (IX).
B, αβ-*Benzotropolone* (XII).
C, 7-*Hydroxybenzo*cyclo*heptatrien*-3-*one* (X).
Solvent: ethanol.

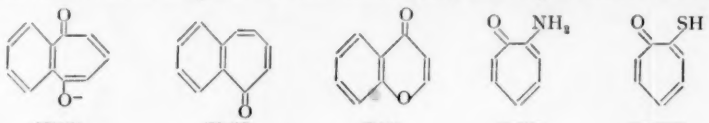
complex, and is not affected by fusion with potassium hydroxide at 220°. Being more acidic than the tropolone (XII) it reacts readily with ethereal diazomethane, and the resulting methyl ether (IX) resembles tropolone methyl ether (Cook, Gibb, Raphael, and Somerville, *J.*, 1951, 503) in forming a stable hemihydrate and in being readily hydrolysed by dilute alkali. During the purification of the methyl ether (IX), a quantity of substance (VII) was isolated, and a fuller examination of this material will be reported later.



Further evidence of similarity between the *iso*tropolone (X) and αβ-benzotropolone (XII) is to be seen in their ultra-violet absorption spectra. The absorption spectrum of the methyl ether (IX) is also given in the Figure.

These results indicate a general similarity between the *iso*tropolone (X) and αβ-benzo-

tropolone (XII), but they do not provide unequivocal evidence of aromatic character. The acidity, salt formation, coupling, and coloration with ferric chloride displayed by (X) may equally be the properties of a conjugated enol-ketone. The fact that (X) is a stronger acid than the tropolone (XII) is to be expected, since resonance in the anion (XIII) involves two identical canonical structures, but the appearance of ketonic properties in (X) requires further comment. It is evident that oxygenated derivatives of benzo*cyclo*heptatrien-3-one (XIV) only show ketonic properties when there is no possibility of hydrogen interaction between the two oxygen atoms. Thus both αβ- and βγ-benzotropolones are devoid of ketonic activity though their methyl ethers, and their isomer (X) gives normal ketone derivatives (Cook, Gibb, Raphael, and Somerville, *ibid.*, 1952, 603; Tarbell and Bill, *J. Amer. Chem. Soc.*, 1952, **74**, 1234). The electronic (+*E*) effect exerted by the hydroxy- or methoxy-groups has no apparent effect on the character of the carbonyl function. In the monocyclic series (II) the evidence is not complete; however, it seems to indicate that in this case the electronic (+*E*) effect of substituents is the important factor. Thus *cyclo*heptatrienone (II) gives ketonic derivatives (Doering, *Chem. Eng. News*, 1953, 2677; Nozoe, *Proc. Japan Acad.*, 1952, **28**, 477), although tropolone (I) and its methyl ether, 2-amino*cyclo*heptatrienone (XVI) (Nozoe, *Sci. Rep. Tohoku*, 1952, **36**, 126) and thiotropolone (XVII) (*idem*, *Proc. Japan Acad.*, 1953, **29**, 22) are all devoid of ketonic properties. Hydrogen bonding has no apparent effect on the character of the carbonyl function. This difference between the monocyclic and the benzo-series, finds a parallel in the chemistry of



(XIII) (XIV) (XV) (XVI) (XVII)

γ-pyrone and its benzo-derivative, chromone (XV). In the former, the electronic (+*E*) effect of the heterocyclic oxygen atom suppresses the ketonic properties of the carbonyl group, but in the latter (XV) its effect is so diminished that normal ketone derivatives are formed (Elderfield, " Heterocyclic Compounds," Wiley and Co., New York, 1951, Vol. 2, p. 254).

Experimental

Benzo*cyclo*heptene-3 : 7-dione (VI) was prepared by the method of Barltrop, Johnson, and Meakins (*J.*, 1951, 181).

*Dehydrogenation of Benzo*cyclo*heptene*-3 : 7-*dione*.—(*a*) A solution of the dione (VI) (2 g.) in 1 : 2 : 4-trichlorobenzene (50 c.c.) was refluxed with palladium–charcoal (5%; 4 g.) for 12 hr. under nitrogen, and the filtered solution extracted with dilute sodium hydroxide solution. Acidification and ether extraction yielded nothing.

(*b*) The dione (VI) (1 g.) in glacial acetic acid (5 c.c.) was treated with bromine (0·95 g., 1·1 mol.) in glacial acetic acid (10 c.c.); when warmed on the steam-bath, the solution became almost colourless, hydrogen bromide was evolved, and the colour reappeared. The solution was concentrated *in vacuo*, made alkaline with sodium hydroxide solution, washed with chloroform, and acidified. This gave a dark intractable gum.

(*c*) A solution of the dione (VI) (2·6 g.) in chloroform (10 c.c.) and carbon tetrachloride (10 c.c.) was refluxed with *N*-bromosuccinimide (2·6 g.) for 15 min. under a 200-watt lamp. The solution was then washed with water and concentrated *in vacuo* to a pale yellow oil. An excess of aqueous trimethylamine was added, and the mixture warmed on the steam-bath for 5 min., and left overnight. The resulting solid *product* crystallised from dilute methanol, and was further purified by chromatography in benzene on alumina. Recrystallisation from ethanol gave plates, m. p. 130—131° (Found: C, 76·8; H, 4·8. $C_{11}H_8O_2$ requires C, 76·7; H, 4·65%). This substance, for which structure (VII) is advanced, gave no picrate, decolorised aqueous potassium permanganate solution very slowly, and was insoluble in sodium hydroxide solution. It failed to give a colour with aqueous or alcoholic ferric chloride, but yielded a *bis*-2 : 4-*dinitrophenylhydrazone* which crystallised from nitrobenzene in scarlet micro-needles, m. p. 318° (decomp.) (Found: N, 20·75. $C_{23}H_{16}O_8N_8$ requires N, 21·05%).

3 : 7-*Diacetoxybenzo*cyclo*hepta*-1 : 3 : 6-*triene* (VIII).—A solution of the dione (VI) (15 g.) and toluene-*p*-sulphonic acid (0·75 g.) in *iso*propenyl acetate (120 c.c.) was refluxed for 16 hr., and

then distilled until 80—100 c.c. had been collected. The residue was dissolved in benzene, and the solution washed with dilute sodium carbonate solution and then with water, and finally concentrated *in vacuo* to an oil. This oil was triturated with ether, the solid *diacetate* filtered off, and the filtrate re-concentrated and re-cycled. From four operations the yield was 15·5 g. The diacetate crystallised from methanol in cream rhombs, m. p. 125—126° (Found: C, 69·6; H, 5·6. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·4%).

7-*Hydroxybenzo*cyclo*heptatrien*-3-*one* (X).—The diacetate (VIII) (3 g.), in carbon tetrachloride (65 c.c.), was heated under reflux with *N*-bromosuccinimide (2·1 g.) and a trace of dibenzoyl peroxide, for 5 hr., under a 200-watt lamp. The solution was then washed with water and concentrated *in vacuo*. The resulting pale yellow oil was heated on the steam-bath for 30 min. with an excess of dilute sodium hydroxide solution and a few drops of ethanol. This gave a dark red solution, which was filtered and acidified. The yellow precipitate was washed, dried on a tile, and sublimed at 150—180°/10^{-4} mm., yielding 0·65 g. of the *hydroxy-ketone*, m. p. 188° (Found: C, 76·6; H, 4·8. $C_{11}H_8O_2$ requires C, 76·7; H, 4·65%). This compound was soluble in sodium hydrogen carbonate solution, and rapidly decolorised aqueous potassium permanganate. It gave a reddish-brown colour with ferric chloride in ethanol, but did not react with copper salts. Its *picrate* crystallised from dilute methanol in yellow needles, m. p. 155—158° (Found: C, 50·65; H, 3·2; N, 10·3. $C_{11}H_8O_2,C_6H_3O_7N_3$ requires C, 50·9; H, 2·7; N, 10·5%); an unstable *hydrochloride* was prepared by passing dry hydrogen chloride through a solution of the hydroxy-ketone in dry acetone; it crystallised from acetone–ether in buff needles, m. p. 150° (decomp.) (Found: C, 58·45; H, 5·1. $C_{11}H_8O_2,HCl,H_2O$ requires C, 58·2; H, 4·9%), and slowly lost hydrochloric acid. On the addition of water, it rapidly reverted to the yellow hydroxy-ketone, m. p. and mixed m. p. 186—188°. Treatment with aqueous perchloric acid gave a brown solution, from which brown needles were obtained by concentration. These decomposed violently when heated. When the hydroxy-ketone was heated with acetic anhydride, it gave an oily product, but on treatment with 3 : 5-dinitrobenzoyl chloride in dry benzene–pyridine, yielded a solid 3 : 5-*dinitrobenzoate*, m. p. 186° (Found: C, 59·3; H, 2·95; N, 7·4. $C_{18}H_{10}O_7N_2$ requires C, 59·0; H, 2·7; N, 7·65%). It also gave a *mono*-2 : 4-*dinitrophenylhydrazone*, m. p. 198° (Found: N, 15·9. $C_{17}H_{12}O_5N_4$ requires N, 15·8%), and reacted readily with ethereal diazomethane, to give an oil *methyl ether hydrate*, b. p. 170—172° (bath)/1·5 mm. (Found: C, 73·85; H, 5·9. $C_{12}H_{10}O_2,\frac{1}{2}H_2O$ requires C, 73·8; H, 5·6%). This ether was readily hydrolysed by aqueous alkali at 100° to the parent hydroxy-ketone (X), and an attempt to form the picrate of the ether gave instead the picrate, m. p. and mixed m. p. 155°, of the hydroxy-ketone. A solid by-product isolated during the purification of the ether crystallised from carbon tetrachloride in needles, m. p. 129—130° (Found: C, 76·6; H, 4·85. Calc. for $C_{11}H_8O_2$: C, 76·7; H, 4·65%). It gave no depression in mixed m. p. with the tricyclic ketone (VII). The hydroxy-ketone (X) in alkaline solution coupled with diazotised aniline, yielding a crimson dye. An electrometric titration carried out on a 30% alcoholic solution, by Dr. J. C. Speakman, indicated a pK value of 6·40. From this, the estimated value in water is *ca.* 6·1.

Hydrogenation.—(*a*) The dione (VI) (1 g.) in ethanol (10 c.c.) was reduced in presence of Adams's (PtO_2) catalyst (0·1 g.). Uptake was rapid until 2 mols. of hydrogen had been absorbed and slow thereafter. Concentration gave the *diol* (XI), which crystallised from aqueous alcohol in needles, m. p. 179—180° (Found: C, 74·4; H, 8·1. $C_{11}H_{14}O_2$ requires C, 74·2; H, 7·9%). The slow uptake probably represents hydrogenolysis of the diol.

(*b*) The hydroxy-ketone (X) (0·1 g.), in ethanol (5 c.c.), was hydrogenated in presence of palladium–calcium carbonate (2%; 0·75 g.). Uptake almost ceased after 3·6 mols. of hydrogen had been absorbed, and the product crystallised in needles, m. p. and mixed m. p. with (XI) 178—179°.

Alkali Fusion.—The hydroxy-ketone (X) (40 mg.) was added to a melt of potassium hydroxide (1 g.) and water (0·3 c.c.), and heated at *ca.* 220° with intermittent stirring for 30 min. After the melt had cooled water was added and the solution was filtered. Acidification yielded starting material, which was identified by mixed m. p.

Absorption Spectra.—These were determined by using a "Unicam" Spectrophotometer.

The author thanks Professor J. W. Cook, F.R.S., for his interest and advice. He is also indebted to Dr. J. C. Speakman for the dissociation-constant determination, and to Drs. J. D. Loudon and R. A. Raphael for helpful discussion. Microanalyses were by Mr. J. M. L. Cameron and Miss M. W. Christie.

UNIVERSITY OF GLASGOW. [*Received, November 13th,* 1953.]

*The β-Phenylserine Series. Part III.**

By Ernst D. Bergmann, H. Bendas, and E. Krakauer.

[Reprint Order No. 4801.]

Condensation of benzaldehyde with glycine gives almost exclusively *erythro*-phenylserine at ≯ −5°, but only the *threo*-form at 30°.

Condensation of glycine ethyl ester with aromatic aldehydes gives, according to the conditions employed, either *threo*- or *erythro*-phenylserine ethyl ester.* Contrary to this experience, it is generally assumed that condensation of benzaldehyde and glycine (Erlenmeyer, *Annalen*, 1899, **307**, 84; 1904, **337**, 222; Erlenmeyer and Fruestueck, *ibid.*, 1895, **289**, 36) gives practically exclusively *threo*-phenylserine, m. p. 196° (decomp.). However, Erlenmeyer has already reported that a second substance, m. p. 187—188°, is also formed, in unspecified yield; it was recently shown by Viscontini and Fuchs (*Helv. Chim. Acta*, 1953, **36**, 660) to be the *erythro*-phenylserine : it was converted by an unambiguous procedure into the *threo*-isomer, and was identical with the product obtained by Chang and Hartung (*J. Amer. Chem. Soc.*, 1953, **75**, 89, 238) from ethyl hydroxyiminobenzoylacetate Ph·CO·C(:N·OH)·CO_2Et by catalytic reduction and subsequent hydrolysis (see Fones, *J. Org. Chem.*, 1952, **17**, 1534; Shaw and Fox, *J. Amer. Chem. Soc.*, 1953, **75**, 3417, 3421; Bolhofer, *ibid.*, 1952, **74**, 5459). The report that *erythro*-phenylserine melts at 260° (Elphimoff-Felkin and Felkin, *Compt. rend.*, 1951, **232**, 241; Elphimoff-Felkin, Felkin, and Tchoubar, and Welvart, *Bull. Soc. chim.*, 1952, 252) is erroneous.

It appeared interesting to study more accurately the stereochemical course of the Erlenmeyer condensation reaction. The Table shows that the reaction is slow at temperatures of 0° and below, but that between 5° and 30° a total yield of phenylserine of 75—90% can be obtained. The composition of this phenylserine depends markedly on the temperature of condensation : at −5° the *erythro*-form is produced almost exclusively; its relative quantity decreases with increasing condensation temperature, until it disappears completely at 30°.

Relative yields (%) *of the isomeric phenylserines.*

Temp. :	−10°	−5°	0°	+5°	+10°	+15°	+20°	+25°	+30°
Crude phenylserine	0	11	28	74	76	81	76	77	90
Ester hydrochlorides (total) *	—	64	60	77	83	84	71	83	82
threo-Salt *	—	2	18	55	54	69	67	78	82
erythro-Salt *	—	62	42	22	29	15	4	5	0

* Calc. on crude phenylserine.

The determination of the relative amounts of the two isomers in the crude phenylserine was based on the observation that the ethyl ester hydrochloride of the *erythro*-form is insoluble in ethyl alcohol, whilst the isomer has a very considerable solubility in this solvent. In the Table the yield of the total ethyl ester hydrochloride is indicated; it is of the order of magnitude of 75%. No attempt has been made to identify the balance of the product obtained in the esterification step.

These observations are of importance in view of the possible synthesis of chloramphenicol from *threo*-phenylserine (Carrara and Weitnauer, *Gazzetta*, 1949, **79**, 854; Vogler, *Helv. Chim. Acta*, 1950, **33**, 2111; Bendas and Bergmann, *Bull. Res. Council Israel*, 1951, **1**, No. 1/2, 131; *J.*, 1951, 2673); for this purpose the condensation of benzaldehyde and glycine is best carried out at 30°. For the preparation of the *erythro*-isomer, the most practical reaction temperature is 5°.

The *threo*-form of phenylserine has also been characterised by a number of derivatives, which are described below.

After this paper had been completed, Shaw and Fox (*locc. cit.*) reported that in the synthesis of phenylserine at 15° (the temperature rising spontaneously to 25—26°) within 1 hr. practically equal quantities of the two isomers were formed but that, when the solution was kept, the quantity of the *erythro*-isomer decreased sharply.

* Part II, *J.*, 1953, 2564.

Experimental

General Procedure.—To the solution of glycine (50 g.) in water (175 ml.) containing sodium hydroxide (41 g.), benzaldehyde (133 g.) was added with vigorous agitation and within a temperature range of ±1°. The temperature was kept constant for 48 hr.; then acetic acid (50 ml.) and water (34 ml.) were added, the temperature being kept at 0—2°. After 12 hr. at 0° the product was filtered off, dissolved in the minimum of boiling water, and precipitated by addition of twice the volume of alcohol and cooling.

This crude phenylserine was dissolved in alcohol, which had been saturated with gaseous hydrogen chloride, and gaseous hydrogen chloride was passed through the solution. On cooling, the *erythro*-ethyl ester hydrochloride crystallised; on concentration, the *threo*-form was obtained. M. p.s were 174° and 138°, respectively. The *erythro*-compound was analysed (Found: C, 53·6; H, 6·6; N, 5·8. Calc. for $C_{11}H_{16}O_3NCl$: C, 53·9; H, 6·5; N, 5·7%).

For the preparation of *erythro*-phenylserine, the following method proved superior to that of Bolhofer (*loc. cit.*) and Elphimoff-Felkin, Tchoubar, and Welvart (*loc. cit.*): the ethyl ester hydrochloride (24·5 g.) was dissolved in 2N-sodium hydroxide (100 ml.). After 30 min. at room temperature, N-hydrochloric acid (100 ml.) was added and the solution was kept for 12 hr. at 0°. Thus, 10 g. (56%) of the desired amino-acid, m. p. 202° (decomp.), were obtained.

For further identification, the following known derivatives were prepared: *ON*-dibenzoylphenylserine ethyl ester, m. p. 167° (from alcohol; *erythro*); *ON*-diacetylphenylserine ethyl ester, m. p. 124° (from *cyclo*hexane; *erythro*), 169—170° (from aqueous alcohol; *threo*); ethyl 2 : 5-diphenyloxazoline-4-carboxylate, m. p. 120° (*erythro*), 86—87° (*threo*). The *threo*-acetyl derivative is obtained only by acetylation at 100°. At the b. p. a compound, m. p. 83°, is formed, which contains one molecule of water less than expected. As this is also obtained from the *erythro*-isomer, it was assumed that it is *ethyl α-diacetylaminocinnamate* (Found: C, 65·8; H, 6·4; N, 5·1; OEt, 16·0. $C_{15}H_{17}O_4N$ requires C, 65·5; H, 6·2; N, 5·1; OEt, 16·3%). The ultra-violet and infra-red absorptions are in accord with this formula. In the latter, the following band assignments can be made: 1700 (Ac_2N and ester-CO); 1460 (Ph); 1380 cm.$^{-1}$ (Me of Ac); owing to conjugation effects, all values are shifted slightly to higher wave-numbers. In the ultra-violet region the compound absorbs at 2780 Å, compared with 2730 Å for cinnamic acid (Landolt-Börnstein, "Tabellen," Vol. II, p. 901, Springer, Berlin, 1923). In order to confirm the assumed formula, the compound was prepared by acetylation of the ethyl ester, prepared from the known (Erlenmeyer and Fruestueck, *loc. cit.*; Bergmann and Delis, *Annalen*, 1927, **458**, 76; Carrara, *Gazzetta*, 1949, **79**, 857) α-acetamidocinnamic acid by alcohol and concentrated sulphuric acid; the *ester* had m. p. 95° (from *cyclo*hexane) (Found: C, 67·1; H, 6·1. $C_{13}H_{15}O_3N$ requires C, 67·0; H, 6·4%).

A mixture of this substance (1 g.), sodium acetate (1 g.), and acetic anhydride (4 ml.), refluxed for 1 hr., gave the diacetyl derivative, m. p. 83° (from 50% alcohol), which did not depress the m. p. of the above compound and showed the identical ultra-violet spectrum (Found: C, 65·4; H, 6·2%).

Similar β-eliminations in α-amino-β-hydroxy-acid derivatives have recently been reported by Riley, Turnbull, and Wilson (*Chem. and Ind.*, 1953, 1180).

threo-ON-*Dibenzoylphenylserine ethyl ester* has been prepared (7 g. from 10 g.) as described for the *erythro*-isomer (Elphimoff-Felkin *et al.*, *loc. cit.*) and had m. p. 156° (from alcohol) (Found: C, 71·9; H, 5·5; N, 3·3. $C_{25}H_{23}O_5N$ requires C, 71·9; H, 5·5; N, 3·3%).

erythro-N-*Dichloroacetylphenylserine.*—Prepared by a Schotten–Baumann reaction at −5° (10 g. from 9 g.), this *compound* melted at 93° after recrystallisation from ether–ligroin (Found: C, 45·0; H, 3·9. $C_{11}H_{11}O_4NCl_2$ requires C, 45·2; H, 4·0%).

threo-N-*Chloroacetylphenylserine*, m. p. 164° (from water) (Found: C, 51·3; H, 4·6. $C_{11}H_{12}O_4NCl$ requires C, 51·3; H, 4·7%), and threo-N-*benzoylphenylserine*, m. p. 159° (from water) (Found: C, 67·3; H, 5·2. $C_{16}H_{15}O_4N$ requires C, 67·4; H, 5·3%), were similarly prepared.

erythro-N-*Chloroacetylphenylserine methyl ester* was prepared by means of boiling methyl chloroacetate (5 min.) and had m. p. 183° (from ethyl alcohol) (Found: C, 52·8; H, 5·5. $C_{12}H_{14}O_4NCl$ requires C, 53·0; H, 5·2%).

Laboratories, Scientific Department,
Israeli Ministry of Defence, Jerusalem.

[*Received, November 16th*, 1953.]

The Chromatography of Gases and Vapours. Part III. The Determination of Adsorption Isotherms.*

By D. H. James and C. S. G. Phillips.

[Reprint Order No. 4812.]

The paper shows how adsorption isotherms can be simply determined by the use of an apparatus designed for gas chromatography. To illustrate the method, the isotherms of benzene and *cyclo*hexane have been determined on charcoal at 77° and at 100°.

In Part II * we described the construction of an apparatus for gas-chromatography, *i.e.*, chromatography in which the moving phase is a gas, and the use of this apparatus for the analysis of mixtures of volatile substances. The chromatographic methods depend upon repeated equilibrations between the moving gas and either a static liquid (partition) or a static solid surface (adsorption). The methods can therefore be used to give information about the equilibria involved, and it is the purpose of this paper to show how this may be done with particular reference to the determination of adsorption isotherms.

There are three basic chromatographic techniques, "elution," "displacement," and "frontal" analysis; each can be used to give information about the equilibria.

(i) *Elution Analysis.*—A sample of the substance is placed at the top of a suitable column, and is then carried down through the column in a slow stream of nitrogen or other inert gas. The sample eventually leaves the bottom of the column in the nitrogen stream, and its concentration is recorded (*e.g.*, by a thermal-conductivity cell) against time. The resulting record will approximate to one of the three types illustrated in Fig. 1. Type *A*, with a sharp concentration front and a trailing rear boundary, indicates an isotherm which curves towards the pressure axis (*e.g.*, Langmuir type). Type *B* indicates an isotherm curving away from the pressure axis, while the symmetrical Gaussian distribution of Type *C* indicates a linear isotherm. A simple elution experiment will thus show at once the type of isotherm involved.

Type *A* is generally the result of adsorption (*e.g.*, on charcoal or silica gel), although water vapour on charcoal at 20° behaves as Type *B* (Phillips, *Discuss. Faraday Soc.*, 1949, **7**, 241). Type *C* is produced by most of the partition columns, provided that the amount of sample used is not too great. As the quantity of sample is increased, the rear boundary sharpens (Type *B*), indicating a curvature of the isotherm away from the pressure axis at high concentrations. An example of this is given in Fig. 2. Fig. 3 illustrates the normal behaviour along a homologous series, where the curvature of the partition isotherm becomes more marked as the molecular weights rise.

With Type *C* the volume of nitrogen passed before the peak appears (retention volume) can be used to give an accurate value for the distribution coefficient of the substance between the gas and the liquid (Martin and Synge, *Biochem. J.*, 1941, **35**, 1358; Martin and A. T. James, *ibid.*, 1952, **50**, 679). An example illustrating the different solubilities of benzene and *cyclo*hexane in a number of solvents was given in Part II (*loc. cit.*).

(ii) *Frontal Analysis.*—The sample is carried on to the column continuously and at a constant concentration in a stream of nitrogen. For a substance having Type *A* behaviour the record is of a single sharp step, produced when the substance breaks through the column. From the time taken before the breakthrough the amount of the substance retained on the column can be determined. (For a mixture of such substances, a series of steps is produced, the number of steps being equal to the number of substances, and each step records the breakthrough from the column of a new component of the mixture.)

In order, therefore, to determine an isotherm point, nitrogen is saturated at a known temperature with the substance under investigation, and is then passed (suitably diluted

* Part II, *J.*, 1953, 1600.

with more nitrogen where necessary) through a weighed quantity of adsorbent. The measurements required are flow-rate, weight of adsorbent, and the time of breakthrough. All these can be made simply and precisely. The sensitivity of the thermal conductivity cell (or other device), which actually records the breakthrough, need not be known, although the constancy of the step height produced on the recorder will be a check on the validity of the method. The only other information required is the vapour pressure of the substance at the saturator temperature. If this is not known, it may be determined as shown below, by displacement analysis.

The practical application of this technique to the determination of the isotherms of benzene and *cyclo*hexane on charcoal at 77° and 100° is given below.

(iii) *Displacement Analysis.*—The mixture to be analysed is placed on top of the column, and is then pushed through the column by means of a displacer vapour, which is

FIG. 1.

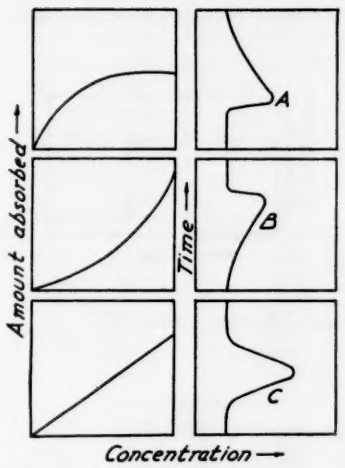


FIG. 2.

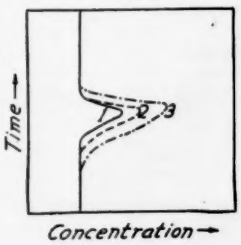


FIG. 3.

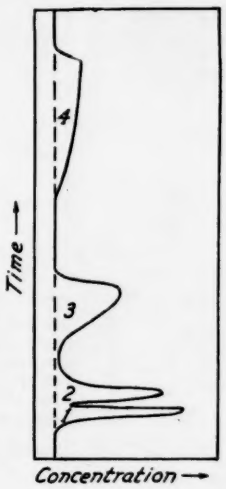


FIG. 1. *Typical elution analyses and related isotherms.*

FIG. 2. *Elution analyses, showing the effect of increased amounts of sample on the shape of the elution zone.*

[Column : 1·5 ml. of Silicone 702, supported on Celite. Temp. : 56°. (1) 0·01 ml., (2) 0·02 ml., (3) 0·04 ml. of ethyl acetate.]

FIG. 3. *Elution analysis of a typical homologous series.*

[Column : 1·5 ml. of tritolyl phosphate, supported on Celite. Temp. : 56°. 0·02 ml. each of (1) methyl acetate, (2) ethyl acetate, (3) propyl acetate, (4) butyl acetate.]

carried at constant concentration in a stream of nitrogen. This displacer must be more strongly adsorbed than any of the components of the mixture. Each component then forms a band of constant concentration on the column, and on leaving the column produces a step in the record of the thermal conductivity cell. When these bands have been established a component is adsorbed on a fraction of the column equal to the time its step eventually takes to leave the column (step length), divided by the breakthrough time of the displacer. The concentration of the vapour in equilibrium with the adsorbed component is the same as the concentration at which the step is formed, and may be simply calculated from the step length, the amount of the component in the mixture, and the nitrogen flow-rate. In this way an isotherm point can be established for each component of the mixture. By altering the nature of the displacer, or its concentration, other points can be determined.

It is to be noted that, as in the method of frontal analysis, the sensitivity of the thermal

conductivity cell is not important. In both methods only Type *A* systems can be satisfactorily studied, and only the ascending isotherm can be determined. No information can be obtained on hysteresis. The displacement method is not suitable in cases of irreversible adsorption.

The diplacement method can also be used for the determination of vapour pressures. Nitrogen, saturated at a known temperature with the substance whose vapour pressure is to be determined, is passed on to a column for a known time. It is then displaced, and the step length determined. This is then compared with a calibrated step obtained by using a known weight of the substance; *e.g.*, for benzene, *cyclo*hexane, and carbon tetrachloride at 15° the ratio of the vapour pressure as determined to that recorded in the literature is 1·00, 0·99, 0·99, respectively.

Experimental

(i) *Apparatus.*—A block diagram of the apparatus is given in Fig. 4. The flow control *F* (James and Phillips, *J. Sci. Instr.*, 1952, **29**, 362), the saturator *S* and column *C* (*idem*, Part II, *loc. cit.*), and the thermal conductivity cell *TC* (Phillips, *loc. cit.*) have been described elsewhere.

Fig. 4.

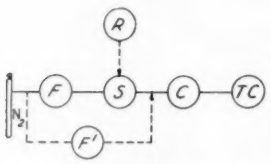


Fig. 5.

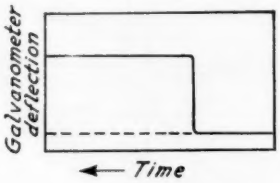


Fig. 4. *Block diagram of apparatus.*

F Flow control.
F' Subsidiary flow control for diluting the main vapour–nitrogen stream.
S Saturator.
R Pressure reducer.
C Chromatographic column.
TC Thermal-conductivity cell.

Fig. 5. *Typical frontal analysis* (*record produced by the thermal conductivity cell*).

The only additional equipment used consisted of a pressure-reducer *R*, attached to the jacket of the saturator, to enable rapid changes of saturator temperature to be made without alteration of the jacketing liquid. This followed the design of Merriman and Wade (*J.*, 1911, **99**, 984), although more recently we have adopted a new design of our own (*J. Sci. Instr.*, in the press). A typical experimental result, *i.e.*, the record produced by the thermal conductivity cell, is shown in Fig. 5.

(ii) *Adsorbent.*—The charcoal used was the same as in the chromatographic analyses, reported in Part II (*loc. cit.*), *viz.*, Sutcliffe Speakman 208C. It was used in a granular form (B.S.S. 30—40) so that the pressure drop across the column was negligible. It was dried at 140° before use.

Results and Discussion

Determination of the Adsorption Isotherms of cyclo*Hexane and Benzene on Charcoal, at* 77° *and at* 100°, *by Frontal Analysis.*—(i) *Calculation.* We use the following symbols: *P*, atmospheric pressure (mm. of Hg); *p*, vapour pressure of adsorbed substance (mm. of Hg) at the saturator temperature; *r*, nitrogen flow-rate into saturator (measured in ml. at room temperature and atmospheric pressure); *t*, breakthrough time (min.) of the substance; *g*, weight of adsorbent (g.); *T*, room temperature (°K); *S*, saturator temperature (°K).

In the following we shall assume that the vapours obey the ideal-gas laws. Reference to tables of generalised compressibility factors (Watson and Smith, *National Petroleum News*, July, 1936) indicates that for *cyclo*hexane and benzene, at the temperatures

concerned, deviations from these laws would lead to a correction of less than 1% at the highest vapour pressures we have used. In the determination of t, a correction was made for the dead volume of the apparatus. This was done by carrying out experiments with different amounts of charcoal in the apparatus. The correction was always less than 0·5 min.

In order to plot the isotherms, we require to know (*a*) the volume v of substance (corrected to S.T.P.) adsorbed per g. of column material at equilibrium, and (*b*) the partial pressure of the substance at the column temperature :

(*a*) v will be given by the relation (flow rate)(concentration of vapour) $\times t/g$, where the flow-rate which we need is the total flow-rate of nitrogen plus vapour leaving the saturator. This will be equal to $r(S/T)[P/(P - p)]$ ml./min. The concentration of vapour in this stream is $p/760$, so that, correcting to standard temperature, we get

$$v = 273rtPp/760gT(P - p) \text{ or } v = KtPp/gT(P - p)$$

(*b*) Although the temperature of the column is in most cases greater than that of the saturator, so that expansion takes place, the partial pressure of the substance will still be p, provided that the gas laws are obeyed. In this connection it is to be noted that the temperature difference between the column and the saturator is only large in the case of small vapour pressures.

(ii) *Results.* In all the experiments the flow rate r was constant at 43·0 ml./min., so the value for the constant K is 15·45. The results are given in Table 1.

TABLE 1.

P	p	T	g		v, ml.	P	p	T	g		v, ml.
		Benzene at 77°						*cyclo*Hexane at 77°			
765	5·70	297°	1·430	279	58·3	760	6·00	297°	1·610	178	34·8
765	26·70	297	1·730	85·6	71·2	762	27·55	297	1·730	54·4	46·7
765	61·55	297	1·440	33·5	81·0	762	63·00	297	1·620	24·3	53·5
765	158·0	297	1·476	13·0	91·3	762	160·0	297	1·580	9·02	60·2
765	262·5	297	14·50	64·7	93·1	762	245·0	297	14·40	49·2	64·0
765	401·1	297	15·90	34·7	95·7	760	360·0	297	15·10	28·1	66·3
765	586·4	297	14·45	10·7	96·2	760	540·8	298	14·90	10·2	67·0
		Benzene at 100°						*cyclo*Hexane at 100°			
753	26·70	297	1·760	74·0	60·6	762	27·55	297	1·740	46·8	40·1
755	58·20	298	1·430	29·5	67·5	762	63·00	297	1·660	21·7	46·7
758	158·9	298	1·280	9·75	79·6	762	160·0	297	1·380	7·20	55·0
765	262·5	298	15·90	67·5	87·8	762	245·0	297	14·60	45·0	57·9
765	424·8	298	14·94	27·5	91·1	760	360·0	297	15·32	26·6	61·9
765	596·0	298	16·00	10·7	93·3	760	540·8	297	15·55	10·4	65·2

(iii) *Discussion.* The isotherms are plotted in Fig. 6. In order to investigate more closely the nature of the adsorption, these results were replotted. Plots of $p/v(p_0 - p)$ against p/p_0 (where p_0 is the saturated vapour pressure at the column temperature), which should be linear for B.E.T. multimolecular adsorption, gave decided curves. Plots of p/v against p, which should be linear for unimolecular (or Langmuir) adsorption, gave good

TABLE 2.

	v_m		b			v_m		b	
	77°	100°	77°	100°		77°	100°	77°	100°
*cyclo*Hexane	68·0	67·1	0·037	0·032	Benzene	99·2	98·3	0·039	0·040

straight lines. These are shown in Fig. 7. From these plots the values of v_m and b of the Langmuir equation were calculated, and are given in Table 2. As the values of v_m are obtained from the slopes of the plots they are more certain than the values of b, which are obtained from the intercepts. The values of b enable a rough estimate of the heats of adsorption to be made. They are found to be of the order of 10 kcal./mole. More accurate values for the heats of adsorption were obtained from the values of p at equal surface coverages at 77° and at 100°. The average values so obtained were 10·4 for benzene and 7·8 kcal./mole for *cyclo*hexane.

We have also calculated the entropies of adsorption at 100°. These do not follow the simple $\boldsymbol{R}$ ln (area) law, suggesting that we have a case of localised adsorption, and we have therefore adopted Everett's procedure (*Trans. Faraday Soc.*, 1950, **46**, 942). Table 3 gives the values of the differential molar entropy ($\Delta\bar{S}$†), and the calculated localisation entropies [$\boldsymbol{R}$ ln $\theta/(1-\theta)$] for different values of θ, the fraction of the surface covered. The difference between these two entropies ($\Delta\bar{S}$*) should be a constant, and represents the loss of entropy on adsorption from a three-dimensional gas at 1 mm. pressure on to the half-covered surface. The average value for benzene is 35, and for *cyclo*hexane 28 entropy units. These values suggest that the motion of the benzene molecule is the more restricted.

FIG. 6.

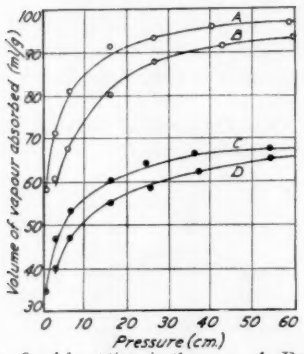


FIG. 7.

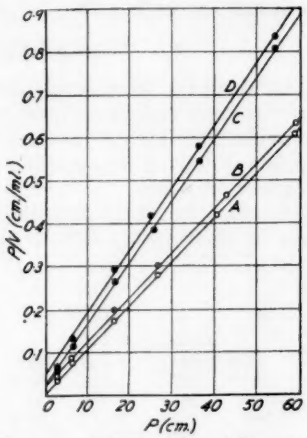


FIG. 6. *Adsorption isotherms*: *A*, Benzene at 77°. *B*, Benzene at 100°. *C*, *cyclo*Hexane at 77°. *D*, *cyclo*Hexane at 100°.

FIG. 7. *Adsorption isotherms, plotted according to the Langmuir equation.*
A, Benzene at 77°. *B*, Benzene at 100°. *C*, *cyclo*Hexane at 77°. *D*, *cyclo*Hexane at 100°.

TABLE 3.

θ	$\Delta\bar{S}$†	$\boldsymbol{R}$ ln $\theta/(1-\theta)$	$\Delta\bar{S}$*	θ	$\Delta\bar{S}$†	$\boldsymbol{R}$ ln $\theta/(1-\theta)$	$\Delta\bar{S}$*
	Benzene				*cyclo*Hexane		
0·62	35·7	1·1	34·6	0·60	27·3	0·9	26·4
0·69	37·0	1·6	35·4	0·70	29·2	1·7	27·5
0·81	38·1	3·0	35·1	0·80	30·8	2·8	28·0
0·89	38·9	4·3	34·6	0·85	31·7	3·5	28·2
0·93	39·9	5·1	34·8	0·90	32·1	4·4	27·7
0·95	40·5	5·9	34·6	0·97	34·0	6·2	27·8

A calculation following Kemball's procedure (*e.g.*, "Advances in Catalysis," Academic Press, New York, 1950, Vol. II, p. 233) gives a value of 32 entropy units for the adsorption as an ideal two-dimensional gas with unrestricted freedom of movement in two directions, and no freedom of movement in a direction perpendicular to the surface.

One of us (D. H. J.) is indebted to the Department of Scientific and Industrial Research for a maintenance grant. We thank Imperial Chemical Industries Limited for the loan of a recorder.

INORGANIC CHEMISTRY LABORATORY, OXFORD. [*Received, November 19th*, 1953.]

Further Investigations of Trifluoromethyldiphenyl Derivatives.

By M. R. Pettit and J. C. Tatlow.

[Reprint Order No. 4858.]

The preparations and some reactions of 2-, 3-, and 4-trifluoromethyldiphenyl are described. 2 : 2′-, 3 : 3′-, and 4 : 4′-Bistrifluoromethyldiphenyl have been made by Ullmann reactions on the corresponding iodobenzotrifluorides. The symmetrical compounds have been characterised by hydrolysis and by nitration to give known diphenyl derivatives.

In an earlier communication (Pettit and Tatlow, *J.*, 1951, 3459), 3-trifluoromethyldiphenyl, 4 : 4′-dinitro-2 : 2′- and -3 : 3′-bistrifluoromethyldiphenyl and some of their derivatives were described. Since that publication, Ross and Kuntz (*J. Amer. Chem. Soc.*, 1952, **74**, 1297) have reported the stepwise reduction of 2 : 2′-dinitro-4 : 4′-bistrifluoromethyldiphenyl to the 2 : 2′-diamino-compound *via* cinnoline intermediates, and the deamination of the diamine to give 4 : 4′-bistrifluoromethyldiphenyl. The last-named compound has also been prepared by Markarian (*ibid.*, p. 1858) from *p*-trifluoromethylphenylmagnesium bromide by the action of silver bromide. 2 : 2′ : 4 : 4′- and 3 : 3′ : 5 : 5′-Tetrakistrifluoromethyldiphenyl were described by Ross, Markarian, and Schwarz (*ibid.*, 1953, **75**, 4967). We now report the preparation and some reactions of the hitherto unknown 2- and 4-trifluoromethyldiphenyl, and of 2 : 2′-, 3 : 3′-, and 4 : 4′-bistrifluoromethyldiphenyl.

The starting materials used in this work, which were prepared by modifications of established routes, included *o*-nitrobenzotrifluoride (cf. Maginnity and Gaulin, *ibid.*, 1951, **73**, 3579), *p*-nitrobenzotrifluoride [prepared from 3-amino-4-nitrobenzotrifluoride (Pouterman and Girardet, *Helv. Chim. Acta*, 1947, **30**, 107) by diazotisation and reaction with hypophosphorous acid], and *o*-, *m*-, and *p*-iodobenzotrifluoride (cf. Finger and Kalinowski, *Trans. Illinois Acad. Sci.*, 1944, **37**, 66; *Chem. Abs.*, 1945, **39**, 1146: Jones, *J. Amer. Chem. Soc.*, 1947, **69**, 2346).

The three trifluoromethyldiphenyls were made by homolytic aromatic substitution reactions *via* the corresponding trifluoromethylbenzenediazo-compounds. During the diazotisation of *o*-aminobenzotrifluoride a little 2 : 2′-bistrifluoromethyldiazoaminobenzene was formed. 2-Trifluoromethyldiphenyl was prepared from the diazonium salt solution by the method of Elks, Haworth, and Hey (*J.*, 1940, 1284). Hydrolysis of this diphenyl with concentrated sulphuric acid (Le Fave, *J. Amer. Chem. Soc.*, 1949, **71**, 4148) yielded 9-oxofluorene, presumably by cyclisation of diphenyl-2-carboxylic acid, [a reaction which is known to proceed readily in the presence of concentrated sulphuric acid (Weger and Döring, *Ber.*, 1903, **36**, 878] or of its acid fluoride.

3-Trifluoromethyldiphenyl, of which a number of syntheses has been reported previously (Bradsher and Bond, *J. Amer. Chem. Soc.*, 1949, **71**, 2659; Pettit and Tatlow, *loc. cit.*), was made also in a manner similar to that which gave the 2-trifluoromethyl isomer. It was shown in the earlier work that the principal product of the mononitration of 3-trifluoromethyldiphenyl was 4-nitro-3′-trifluoromethyldiphenyl (*idem*, *loc. cit.*). A further examination of this reaction has shown that a second isomer, 2-nitro-3′-trifluoromethyldiphenyl, is also formed. Evidence about the structure of this isomer was provided by reduction to a crude amine, from which *m*-trifluoromethylbenzoic acid was obtained upon oxidation. This showed that the trifluoromethyl and the amino-group were on different rings. The structure of the compound was proved completely by hydrolysis of the trifluoromethyl group to carboxyl; the product was the known 2-nitrodiphenyl-3′-carboxylic acid (Adams and Cairns, *J. Amer. Chem. Soc.*, 1939, **61**, 2179). Further nitration, with nitric acid–sulphuric acid, of 2-nitro-3′-trifluoromethyldiphenyl yielded a trinitro-derivative, identical with the product which we have previously described (*loc. cit.*). This compound must therefore be 2 : 4 : 4′-trinitro-3′-trifluoromethyldiphenyl since it can be prepared also from 4 : 4′-dinitro-3-trifluoromethyldiphenyl, which was itself derived from

both 4- and 4′-nitro-3-trifluoromethyldiphenyl. Hence the position of each nitro-group of the trinitro-derivative has been established separately.

4-Trifluoromethyldiphenyl was made from *p*-acetamidobenzotrifluoride which was converted into the *N*-nitroso-derivative with nitrous fumes; this was allowed to decompose in benzene (Bamberger, *Ber.*, 1897, **30**, 366; Haworth and Hey, *J.*, 1940, 361). Nitrosation of *p*-acetamidobenzotrifluoride was also effected by trifluoroacetic anhydride–ethyl nitrite, which can nitrosate reactive aromatic compounds (Bourne, Stacey, Tatlow, and Tedder, *J.*, 1952, 1695). In addition, 4-trifluoromethyldiphenyl was prepared by diazotisation, in aqueous trifluoroacetic acid (Pettit, Stacey, and Tatlow, *J.*, 1953, 3081), of *p*-aminobenzotrifluoride, followed by the stirring together of benzene and the aqueous acidic diazonium solution so formed. The last two syntheses are examples of general reactions which diazonium derivatives of trifluoroacetic acid and other perhalogenocarboxylic acids will undergo (Pettit and Tatlow, forthcoming publication). Nitration of 4-trifluoromethyldiphenyl gave 4-nitro-4′-trifluoromethyldiphenyl, which, on hydrolysis, afforded the known 4′-nitrodiphenyl-4-carboxylic acid.

When heated with copper bronze (Ullmann and Bielecki, *Ber.*, 1901, **34**, 2174), *o*-, *m*-, and *p*-iodobenzotrifluoride were converted into 2 : 2′-, 3 : 3′-, and 4 : 4′-bistrifluoromethyldiphenyl, respectively. Finger and Kalinowski (*loc. cit.*) have reported that *m*-iodobenzotrifluoride would not undergo the Ullmann reaction to form a diphenyl with copper bronze at 250—270° (presumably in a sealed tube). The sample of 2 : 2′-bistrifluoromethyldiphenyl so prepared was identical with that obtained by deamination of 4 : 4′-diamino-2 : 2′-bistrifluoromethyldiphenyl which had been made *via* a benzidine transformation on the hydrazo-compound obtained by reduction of *m*-nitrobenzotrifluoride (Cartwright and Tatlow, *J.*, 1953, 1994). On hydrolysis with sulphuric acid, 2 : 2′-bistrifluoromethyldiphenyl gave the expected 9-oxofluorene-4-carboxylic acid and, in addition, a neutral compound (*idem*, *loc. cit.*). This has now been identified as 9-oxo-4-trifluoromethylfluorene, since it gave an oxime and was hydrolysed further with sulphuric acid to the oxofluorenecarboxylic acid. 3 : 3′- (Bradsher and Bond, *loc. cit.*; Markarian, *loc. cit.*) and 4 : 4′-bistrifluoromethyldiphenyl (Ross and Kuntz, *loc. cit.*; Markarian, *loc. cit.*) gave, on hydrolysis, diphenyl-3 : 3′- and -4 : 4′-dicarboxylic acid, respectively. These acids were characterised as ester derivatives. In the cases of the trifluoromethyl- and bistrifluoromethyl-diphenyls, as in other series, hydrolysis of the trifluoromethyl groups (Le Fave, *loc. cit.*) is a useful aid to structural determinations.

Nitration of the symmetrical bistrifluoromethyldiphenyls gave the expected dinitro-compounds, all of which have been synthesised previously by other methods. The 2 : 2′-isomer gave 4 : 4′-dinitro-2 : 2′-bistrifluoromethyldiphenyl, and the 3 : 3′-isomer afforded 4 : 4′-dinitro-3 : 3′-bistrifluoromethyldiphenyl (Pettit and Tatlow, *loc. cit.*), whilst 2 : 2′-dinitro-4 : 4′-bistrifluoromethyldiphenyl (Bradsher and Bond, *loc. cit.*; Ross and Kuntz, *loc. cit.*) was obtained from the 4 : 4′-isomer.

Experimental

p-*Nitrobenzotrifluoride*.—3-Amino-4-nitrobenzotrifluoride (Pouterman and Girardet, *loc. cit.*) (25·1 g.), in glacial acetic acid (100 c.c.) and concentrated sulphuric acid (25 c.c.), was diazotised at 10° with saturated aqueous sodium nitrite. Hypophosphorous acid (30%; 80 c.c.) was added, and after 5 hr. at *ca.* 15° the mixture was heated to 100° for 15 min., cooled, and poured into ice-water. The precipitate was filtered off and distilled in steam to give *p*-nitrobenzotrifluoride (67%), m. p. 37—39°.

A similar reaction with 5-amino-2-nitrobenzotrifluoride gave the *o*-nitro-isomer (69%).

o-*Aminobenzotrifluoride*.—Reduction of a solution of *o*-nitrobenzotrifluoride (22·0 g.) in dioxan (100 c.c.) by hydrogen over Raney nickel in a stirred autoclave (20 atm.; 180°), gave, upon fractionation of the product, *o*-aminobenzotrifluoride (14·7 g.), b. p. 72—74°/21 mm. The b. p. is identical with that recorded by Jones (*loc. cit.*).

Preparation of 2-*Trifluoromethyldiphenyl*.—*o*-Aminobenzotrifluoride (24·4 g.) was diazotised in concentrated hydrochloric acid (45 c.c.) and water (25 c.c.) with aqueous sodium nitrite (40%). A small quantity of yellow solid separated; it was filtered off and recrystallised from light petroleum (b. p. 100—120°), giving 2 : 2′-*bistrifluoromethyldiazoaminobenzene*, m. p. 170—171·5° (Found: C, 50·8; H, 2·8. $C_{14}H_9N_3F_6$ requires C, 50·5; H, 2·7%). The filtrate, which

contained 2-trifluoromethylbenzenediazonium chloride, was stirred at 0—5° with benzene (200 c.c.), and a solution of sodium acetate trihydrate (70 g.) in water (150 c.c.) was added slowly. Stirring was continued for 2 hr. at 0°, and then at 10—15° for a further 46 hr. The benzene layer was separated, washed with water, dried ($MgSO_4$), and evaporated to remove the solvent. Distillation of the residue at reduced pressure yielded a pale yellow liquid, b. p. 122—125°/23 mm., which solidified almost completely in an ice-bath. The few drops of syrupy material were removed by filtration through a cooled funnel. Redistillation of the residue afforded *2-trifluoromethyldiphenyl* (12·6 g.), b. p. 114°/19 mm., m. p. 15° (Found: C, 70·4; H, 4·2; F, 26·2. $C_{13}H_9F_3$ requires C, 70·3; H, 4·1; F, 25·6%).

Conversion of 2-Trifluoromethyldiphenyl into 9-Oxofluorene.—2-Trifluoromethyldiphenyl (0·58 g.) was stirred with concentrated sulphuric acid (0·7 c.c.) at 100° for 1 hr., after which time evolution of hydrogen fluoride appeared to have ceased. The residual black liquid was poured into water (30 c.c.), and the resultant yellow suspension was extracted with ether. The extracts were washed with sodium hydroxide solution and with water, dried ($MgSO_4$), and evaporated. The yellow residue, on recrystallisation from benzene–light petroleum (b. p. 60—80°), gave 9-oxofluorene (0·12 g.), m. p. and mixed m. p. 81—83° (Found: C, 86·4; H, 4·8. Calc. for $C_{13}H_8O$: C, 86·6; H, 4·5%). Weger and Döring (*loc. cit.*) recorded m. p. 83—84° for this compound.

Preparation of 3-Trifluoromethyldiphenyl.—*m*-Aminobenzotrifluoride was diazotised as for the *o*-isomer (no diazoamino-compound was formed) and by the procedure described above 3-trifluoromethyldiphenyl (39%), b. p. 115—118°/13 mm., was obtained. The product solidified on nucleation with a specimen of the material previously reported (Pettit and Tatlow, *loc. cit.*). Despite our earlier experience which suggested the contrary, this method is at least as satisfactory for the production of this compound as is that by using the nitrosoacetanilide (*idem, loc. cit.*).

Nitration of 3-Trifluoromethyldiphenyl.—A stirred solution of 3-trifluoromethyldiphenyl (22·5 g.) in glacial acetic acid (30 c.c.) was cooled to 0°, and a mixture of fuming nitric acid (6·2 c.c.; *d*, 1·5) and concentrated sulphuric acid (5·0 c.c.) was added. The reactants were heated slowly, finally being gently refluxed for 45 min., stirring being continued. When cool, the mixture was poured into water (250 c.c.), and the semi-solid mass was extracted with ether. After being washed with dilute sodium hydroxide solution and with water, the extract was dried ($MgSO_4$), and the ether was removed by distillation. The residue was dissolved in hot ethyl alcohol, and the solution was cooled to 0°. The crystals which separated were filtered off and washed with more cooled alcohol (10 c.c.) to give 4-nitro-3′-trifluoromethyldiphenyl (10·8 g.), m. p. 83—85° not depressed by a specimen (m. p. 86°) previously described (Pettit and Tatlow, *loc. cit.*). The filtrate was concentrated and the oil remaining was distilled to give (*a*) a small amount of 3-trifluoromethyldiphenyl (1·0 g.), b. p. 70—87°/1 mm., (*b*) a pale yellow liquid (10·1 g.), b. p. 118—121°/0·2—0·3 mm., and (*c*) material of higher b. p., which on recrystallisation afforded more 4-nitro-3′-trifluoromethyldiphenyl (2·4 g.), m. p. and mixed m. p. 85°. Fraction (*b*) very slowly crystallised; the solid was recrystallised from light petroleum (b. p. 60—80°), affording very pale yellow prisms of *2-nitro-3′-trifluoromethyldiphenyl*, m. p. 60—61·5° (Found: C, 58·4; H, 2·7; F, 21·8. $C_{13}H_8O_2NF_3$ requires C, 58·4; H, 3·0; F, 21·3%). The m. p. was depressed in admixture with the 4-nitro-isomer.

Hydrolysis of 2-Nitro-3′-trifluoromethyldiphenyl.—The nitro-compound (2·25 g.) and concentrated sulphuric acid (5·0 c.c.) were stirred and heated at 130—150° for 1 hr. in an open tube. Hydrogen fluoride was evolved and the reaction mixture darkened. Water (100 c.c.) was added to the cooled mixture, and the resultant white precipitate was recrystallised from aqueous ethyl alcohol, giving 2-nitrodiphenyl-3′-carboxylic acid (1·95 g.), m. p. 208—209° unchanged by sublimation under reduced pressure (Found: C, 64·3; H, 3·8. Calc. for $C_{13}H_9O_4N$: C, 64·2; H, 3·7%). The m. p. was undepressed in admixture with the specimen described below.

Preparation of Ethyl m-*Iodobenzoate* (*By Le Fave and Scheurer's process*; J. Amer. Chem. Soc., 1950, **72**, 2464).—*m*-Iodobenzotrifluoride (11·4 g.) and concentrated sulphuric acid (8·0 c.c.) were mechanically stirred, and heated on an oil-bath. At about 120° hydrogen fluoride was evolved, and this temperature was maintained for 45 min. The mixture was then heated under reflux with ethyl alcohol (50 c.c.) for 30 min., the solution was poured into water, neutralised with sodium hydrogen carbonate, and extracted with chloroform, and the extracts were dried ($MgSO_4$), evaporated, and distilled under reduced pressure to give ethyl *m*-iodobenzoate (6·9 g.), b. p. 164—165°/23 mm. Cohen and Raper (*J.*, 1904, 1271) recorded b. p. 165—166°/24 mm. for this compound.

Preparation of 2-Nitrodiphenyl-3′-carboxylic Acid.—The above ester (6·8 g.), when heated

with *o*-bromonitrobenzene (6·4 g.) and activated copper bronze (12 g.), under the conditions described by Adams and Cairns (*loc. cit.*), yielded 2-nitrodiphenyl-3′-carboxylic acid (1·49 g.), m. p. 206—208° not depressed by the material prepared as described above.

Degradation of 2-*Nitro*-3′-*trifluoromethyldiphenyl to* m-*Trifluoromethylbenzoic Acid.*—2-Nitro-3′-trifluoromethyldiphenyl (0·690 g.) was reduced with granulated tin (4 g.), concentrated hydrochloric acid (15 c.c.), water (5 c.c.), and ethyl alcohol (5 c.c.). After being worked up in the usual way, an almost colourless syrup (0·540 g.) was obtained. This crude 2-amino-3′-trifluoromethyldiphenyl (0·430 g.) was oxidised in solution in concentrated sulphuric acid (2·0 c.c.) and water (5 c.c.) with potassium permanganate (3·44 g.). Isolation as already described (Pettit and Tatlow, *loc. cit.*) for a similar reaction afforded *m*-trifluoromethylbenzoic acid (0·100 g.), m. p. and mixed m. p. 103—104°.

Preparation of 2 : 4 : 4′-*Trinitro*-3′-*trifluoromethyldiphenyl.*—2-Nitro-3′-trifluoromethyldiphenyl (0·233 g.) was heated under reflux with concentrated sulphuric acid (1·0 c.c.) and concentrated nitric acid (1·0 c.c.) for 40 min. The cooled mixture was treated with water (20 c.c.) and extracted with ether. The extract was washed with aqueous sodium hydroxide and with water, and was then dried ($MgSO_4$). Evaporation of the solvent, followed by recrystallisation from ethyl alcohol, yielded 2 : 4 : 4′-trinitro-3′-trifluoromethyldiphenyl (0·231 g.), m. p. 152—154° not depressed in admixture with the trinitro-3-trifluoromethyldiphenyl previously reported (Pettit and Tatlow, *loc. cit.*).

Preparation of 4-*Trifluoromethyldiphenyl.*—(*a*) *p*-Acetamidobenzotrifluoride (Jones, *loc. cit.*) (5·0 g.) was dissolved in glacial acetic acid (25 c.c.) and treated with nitrous fumes at 10°. When the deep clear green colour had developed (*ca.* 4 hr.), the solution was poured into water, and the precipitate filtered off, dried on a porous plate, and stirred with benzene (50 c.c.) for 24 hr. at *ca.* 15°. The crystalline material remaining after this treatment was unchanged *p*-acetamidobenzotrifluoride (1·94 g.), m. p. 146—150°. After removal of the benzene, the residue was distilled at reduced pressure, and any *p*-acetamidobenzotrifluoride remaining removed by hydrolysis with aqueous-alcoholic hydrochloric acid. Recrystallisation of the crude product yielded 4-*trifluoromethyldiphenyl* (1·5 g.), m. p. 70° (Found: C, 70·3; H, 4·2; F, 25·9. $C_{13}H_9F_3$ requires C, 70·3; H, 4·1; F, 25·6%).

(*b*) Trifluoroacetic anhydride (1·8 c.c.) was added to ethyl nitrite (0·95 c.c.) at the temperature of an ice–salt bath. After 5 min., dry *p*-acetamidobenzotrifluoride (1·48 g.) was added portionwise, with shaking between the additions. The solution so obtained was then stirred with benzene (25 c.c.) for 24 hr. at 10—15°. Volatile constituents were removed by distillation at 100° under slightly reduced pressure, and the residue was steam-distilled. The distillate was extracted with ether, and after being dried ($MgSO_4$) the extracts were evaporated. Recrystallisation of the crude material from aqueous ethyl alcohol gave 4-trifluoromethyldiphenyl (0·37 g.), m. p. and mixed m. p. 70°.

(*c*) *p*-Aminobenzotrifluoride (1·80 g.) was diazotised in trifluoroacetic acid (2·5 c.c.) and water (1·0 c.c.) with 40% aqueous sodium nitrite, and the diazonium solution was stirred with benzene (25 c.c.) for 24 hr. at 25°. The organic layer was then separated, washed with dilute sodium hydroxide solution (3 times) and with water, and then distilled, steam-distilled, and treated as above. On recrystallisation from aqueous ethyl alcohol, 4-trifluoromethyldiphenyl (0·41 g.), m. p. and mixed m. p. 70°, was obtained.

Nitration of 4-*Trifluoromethyldiphenyl.*—4-Trifluoromethyldiphenyl (0·92 g.), glacial acetic acid (5·0 c.c.), fuming nitric acid (0·30 c.c., *d*, 1·5), and concentrated sulphuric acid (0·50 c.c.) were heated under reflux for 30 min. Isolation as usual and recrystallisation from aqueous ethyl alcohol afforded 4-*nitro*-4′-*trifluoromethyldiphenyl* (0·45 g.), m. p. 121—122° (Found: C, 58·7; H, 2·9. $C_{13}H_8O_2NF_3$ requires C, 58·4; H, 3·0%).

Hydrolysis of 4-*Nitro*-4′-*trifluoromethyldiphenyl.*—The nitro-compound (0·120 g.) was stirred for 45 min. with concentrated sulphuric acid (0·40 c.c.) at 120—130°. The product was poured into water and extracted with ether. Recrystallisation, from aqueous ethyl alcohol, of the residue obtained by evaporation of the extracts yielded 4-nitrodiphenyl-4′-carboxylic acid (0·035 g.), m. p. 338—340° (Found: C, 64·5; H, 4·1. Calc. for $C_{13}H_9O_4N$: C, 64·2; H, 3·7%). Grieve and Hey (*J.*, 1932, 1888) reported m. p. 340° for this acid.

Preparation of 2 : 2′-*Bistrifluoromethyldiphenyl.*—*o*-Iodobenzotrifluoride (Jones, *loc. cit.*) (11·9 g.) was refluxed with copper bronze (4·2 g.) for 12 hr. with occasional stirring. When cool, the inorganic material was filtered off, and washed several times with ether. The combined filtrates were evaporated and the residue was distilled at atmospheric pressure to give an almost colourless liquid (4·80 g.), b. p. 233—237°, which crystallised. Recrystallisation from aqueous ethyl alcohol afforded 2 : 2′-bistrifluoromethyldiphenyl, m. p. 32—33°, b. p. 236—

237° (Found: C, 58·2; H, 2·8; F, 39·3. Calc. for $C_{14}H_8F_6$: C, 57·9; H, 2·8; F, 39·3%). Nucleation by a crystal of this compound caused solidification of material previously obtained by deamination of 4 : 4′-diamino-2 : 2′-bistrifluoromethyldiphenyl (Cartwright and Tatlow, *loc. cit.*).

Action of Sulphuric Acid on 2 : 2′-Bistrifluoromethyldiphenyl.—2 : 2′-Bistrifluoromethyldiphenyl (0·88 g.) and concentrated sulphuric acid (0·9 c.c.) were heated at 100° for 1 hr. with vigorous stirring. The mixture was then treated with water (70 c.c.) and extracted with ether. The extract was washed with portions of dilute sodium hydroxide solution until the aqueous phase was colourless. After being washed with water, the ether was dried ($MgSO_4$) and evaporated. By recrystallisation of the residue from ethyl alcohol, *9-oxo-4-trifluoromethylfluorene* (0·42 g.), m. p. 125—126°, was obtained (Found: C, 67·9; H, 2·7; F, 22·8. $C_{14}H_7OF_3$ requires C, 67·7; H, 2·8; F, 23·0%). This compound, on treatment with hydroxylamine, afforded the *oxime*, m. p. 165—166° (from aqueous ethyl alcohol) (Found: C, 63·6; H, 3·4. $C_{14}H_8ONF_3$ requires C, 63·9; H, 3·1%).

The alkaline washings of the ethereal phase were acidified with concentrated hydrochloric acid. A yellow precipitate formed, and was filtered off and recrystallised to give 9-oxofluorene-4-carboxylic acid (0·14 g.), m. p. and mixed m. p. 226—227° (Found: C, 75·2; H, 3·7. Calc. for $C_{14}H_8O_3$: C, 75·0; H, 3·6%). Graebe and Aubin (*Ber.*, 1887, **20**, 845) gave m. p. 227° for this compound.

Hydrolysis of 9-Oxo-4-trifluoromethylfluorene.—Hydrolysis of 9-oxo-4-trifluoromethylfluorene (0·060 g.) by 85% sulphuric acid (1·0 c.c.) during 1 hr. at 120—130°, afforded, after isolation as above, unchanged ketone (0·028 g.) and 9-oxofluorene-4-carboxylic acid (0·011 g.), m. p. and mixed m. p. 225—227°.

Nitration of 2 : 2′-Bistrifluoromethyldiphenyl.—2 : 2′-Bistrifluoromethyldiphenyl (0·91 g.) was stirred at room temperature with concentrated sulphuric acid (6·0 c.c.), and fuming nitric acid (*d* 1·5; 0·40 c.c.) was added slowly. After being stirred for 16 hr., the mixture was treated with water (40 c.c.) and extracted with ether. The extract was washed with dilute sodium hydroxide, and then with water, and was dried ($MgSO_4$). The solvent was evaporated and the residue recrystallised from aqueous ethyl alcohol, giving light yellow crystals of 4 : 4′-dinitro-2 : 2′-bistrifluoromethyldiphenyl (0·63 g.), m. p. 137·5—138·5° (Found: C, 44·3; H, 1·8. Calc. for $C_{14}H_6O_4N_2F_6$: C, 44·2; H, 1·6%). Pettit and Tatlow (*loc. cit.*) recorded m. p. 137·5° for this compound.

Preparation of 3 : 3′-Bistrifluoromethyldiphenyl.—*m*-Iodobenzotrifluoride (b. p. 176—178°; Finger and Kalinowski, *loc. cit.*, recorded b. p. 173°) (23·5 g.) was heated under gentle reflux with copper bronze (8·15 g.) for 19 hr. with occasional stirring. The product was treated as for the 2 : 2′-isomer above, to give an almost colourless liquid (8·79 g.), b. p. 231—242°, which crystallised. Recrystallisation of a sample from aqueous ethyl alcohol gave needles of 3 : 3′-bistrifluoromethyldiphenyl, m. p. 24·5—26°, b. p. 237—240° (Found: C, 58·2; H, 3·0; F, 39·2. Calc. for $C_{14}H_8F_6$: C, 57·9; H, 2·8; F, 39·3%). Bradsher and Bond (*loc. cit.*) cited b. p. 93—94°/3 mm.

Hydrolysis of 3 : 3′-Bistrifluoromethyldiphenyl.—Hydrolysis of 3 : 3′-bistrifluoromethyldiphenyl (1·13 g.) by concentrated sulphuric acid (0·7 c.c.) at 130—150° for 1 hr. yielded, by the usual method of isolation, diphenyl-3 : 3′-dicarboxylic acid (0·38 g.), m. p. 346—348°. Williamson and Rodebush (*J. Amer. Chem. Soc.*, 1941, **63**, 3018) recorded m. p. 350—352° for this compound. Unchanged 3 : 3′-bistrifluoromethyldiphenyl (0·48 g.) was recovered.

Esterification by Bülow and Reden's technique (*Ber.*, 1898, **31**, 2574) afforded the diethyl ester, m. p. 68°. Bülow and Reden reported m. p. 68° for this ester.

Nitration of 3 : 3′-Bistrifluoromethyldiphenyl.—3 : 3′-Bistrifluoromethyldiphenyl (1·40 g.) was stirred for 12 hr. at room temperature with concentrated sulphuric acid (10 c.c.) and fuming nitric acid (*d* 1·5; 0·50 c.c.). The mixture was worked up as in the case of the 2 : 2′-bistrifluoromethyl isomer, and on recrystallisation from ethyl alcohol, 4 : 4′-dinitro-3 : 3′-bistrifluoromethyldiphenyl (0·98 g.) was obtained, m. p. 180—181° [alone or in admixture with material prepared by an Ullmann reaction on 5-iodo-2-nitrobenzotrifluoride (Pettit and Tatlow, *loc. cit.*)] (Found: C, 44·5; H, 1·3. Calc. for $C_{14}H_6O_4N_2F_6$: C, 44·2; H, 1·6%).

Preparation of 4 : 4′-Bistrifluoromethyldiphenyl.—*p*-Iodobenzotrifluoride (2·30 g.) and copper bronze (0·78 g.) were gently refluxed for 24 hr. An ethereal solution of the product was filtered and evaporated; recrystallisation of the residue from aqueous ethyl alcohol afforded 4 : 4′-bistrifluoromethyldiphenyl (0·51 g.), m. p. 92—93° (Found: C, 58·1; H, 3·1; F, 38·7. Calc. for $C_{14}H_8F_6$: C, 57·9; H, 2·8; F, 39·3%). Ross and Kuntz (*loc. cit.*) recorded m. p. 93—94·5° for this compound, while Markarian (*loc. cit.*) cited 91—92°.

Hydrolysis of 4 : 4′-*Bistrifluoromethyldiphenyl.*—4 : 4′-Bistrifluoromethyldiphenyl (0·051 g.) was hydrolysed by concentrated sulphuric acid (0·4 c.c.) at 100° for 1 hr. By the usual method of extraction, diphenyl-4 : 4′-dicarboxylic acid (0·037 g.), which did not melt below 360° (cf. Doebner, *Annalen*, **1874**, **172**, 109), was obtained. The crude acid was converted into the acid chloride by Work's method (*J.*, 1940, 1315). Methyl alcohol (1·0 c.c.) was added to the unpurified product, and the mixture was heated under reflux for 15 min. By recrystallisation from benzene, dimethyl diphenyl-4 : 4′-dicarboxylate (0·011 g.), m. p. 214°, was obtained (Found: C, 71·4; H, 4·9. Calc. for $C_{16}H_{14}O_4$: C, 71·1; H, 5·2%). Ullmann and Meyer (*Annalen*, 1901, **332**, 73) cited m. p. 214° for this ester.

Nitration of 4 : 4′-*Bistrifluoromethyldiphenyl.*—The diphenyl derivative (0·086 g.) was stirred for 1 hr. with concentrated sulphuric acid (2·0 c.c.) and fuming nitric acid (*d* 1·5; 0·30 c.c.). Treatment as in the case of the 2 : 2′-bistrifluoromethyl isomer afforded 2 : 2′-dinitro-4 : 4′-bistrifluoromethyldiphenyl (0·082 g.), m. p. 121·5—123° (after recrystallisation from ethyl alcohol) (Found: C, 44·5; H, 1·7. Calc. for $C_{14}H_6O_4N_2F_6$: C, 44·2; H, 1·6%). Bradsher and Bond (*loc. cit.*) recorded m. p. 121—122°, and Ross and Kuntz (*loc. cit.*), m. p. 124—125°, for this compound.

The authors thank Professor M. Stacey, F.R.S., for his interest. The expenses of the investigation were covered by a grant from the Research Fund of the University.

CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM 15. [*Received, December 2nd,* 1953.]

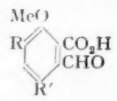
Phthalaldehydes and Related Compounds. Part IV. Synthesis of Gladiolic Acid.*

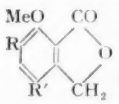
By J. J. BROWN and G. T. NEWBOLD.

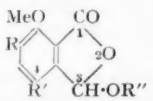
[Reprint Order No. 4896.]

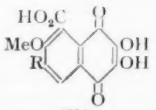
Gladiolic acid has been obtained by periodate oxidation of deoxygladiolic acid (4-formyl-7-methoxy-6-methylphthalide) (cf. *Chem. and Ind.*, 1953, 1151).

THE structure of gladiolic acid, an antifungal metabolic product from *Penicillium gladioli* Machacek, is represented by (I; R = Me, R′ = CHO) tautomeric with (III; R = Me, R′ = CHO, R″ = H) as a result of analytical and degradation evidence (Grove, *Biochem. J.*, 1952, **50**, 648; *J*, 1952, 3345; Raistrick and Ross, *Biochem. J.*, 1952, **50**, 635). In Part III *


(I)


(II)


(III)


(IV)

we described a synthesis of deoxygladiolic acid (II; R = Me, R′ = CHO) (Grove, *Biochem. J.*, 1952, 648) by the action of *N*-bromosuccinimide on 4-hydroxymethyl-7-methoxy-6-methylphthalide (II; R = Me, R′ = CH_2·OH), followed by hydrolysis (Brown and Newbold, *J.*, 1953, 1285). An attempt to convert (II; R = Me, R′ = CH_2Cl) into gladiolic acid by the same reagent (*idem*, *J.*, 1953, 3648) was unsuccessful, the products being deoxygladiolic acid and *iso*gladiolic acid (II; R = Me, R′ = CO_2H) (Grove, *loc. cit.*); a trace of gladiolic acid, insufficient for isolation, was also formed. Thus negligible attack by *N*-bromosuccinimide on the methylene group of (II; R = Me, R′ = CH_2Cl) occurred, in marked contrast to the behaviour of 4-chloromethylmeconin (II; R = OMe, R′ = CH_2Cl) which under these conditions gave a good yield of 3-formylopianic acid (I; R = OMe, R′ = CHO) tautomeric with (III; R = OMe, R′ = CHO, R″ = H) (Brown and Newbold, *J.*, 1952, 4878).

Dihydrogladiolic acid, also produced by *Penicillium gladioli* Machacek, has been shown to be (I; R = Me; R′ = CH_2·OH), tautomeric with (III; R = Me, R′ = CH_2·OH,

* Part III, *J.*, 1953, 3648.

R″ = H) (Duncanson, Grove, and Zealley, *J.*, 1953, 3637; Brown and Newbold, *J.*, 1953, 3648). Raistrick and Ross (*loc. cit.*) oxidised it by periodate to gladiolic acid, *i.e.*, a phthalaldehyde was formed from an *o*-hydroxymethylbenzaldehyde. Since deoxygladiolic acid (II; R = Me, R′ = CHO) has the related 4-formylphthalide system, attention was turned to periodate oxidation of this compound. Prolonged oxidation with sodium metaperiodate in boiling dilute sulphuric acid partly converted it into gladiolic acid and *iso*gladiolic acid. Deoxygladiolic acid (73%) was recovered, and the gladiolic acid was isolated as its hydrate triacetate [III; R = Me, R′ = $CH(OAc)_2$, R″ = Ac] which was obtained in 10% yield calculated on the deoxygladiolic acid converted. The triacetate was smoothly hydrolysed to gladiolic acid by hot mineral acid. Both the latter and the triacetate were indistinguishable from the natural material (supplied by Mr. J. F. Grove) and its derivative respectively. *iso*Gladiolic acid was isolated, in 40% yield calculated on the deoxygladiolic acid converted, from the acid fraction of the acetylation mixture. Gladiolic acid has been transformed into dihydrogladiolic acid (I; R = Me, R′ = CH_2·OH) by successive acetylation [to give (III; R = Me, R′ = CHO, R″ = Ac)], hydrogenation [to (III; R = Me, R′ = CH_2·OH, R″ = Ac)], and hydrolysis of the 3-acetoxy-group (Duncanson, Grove, and Zealley, *loc. cit.*); our synthesis of gladiolic acid is therefore a formal synthesis of dihydrogladiolic acid.

Oxidation of 4-formylmeconin (II; R = OMe, R′ = CHO), whose preparation was described in Part III, with periodate proceeded much more rapidly than that of deoxygladiolic acid; 71% of the material was recovered and 3-formylopianic acid (I; R = OMe, R′ = CHO) was readily isolated in 40% yield calculated on the 4-formylmeconin transformed. This again illustrates the greater reactivity of the lactone methylene group towards an oxidising agent in the dimethoxy-series. Presence of the phthalaldehyde system in 3-formylopianic acid has been proved directly by reaction with glyoxal in mildly alkaline solution in the presence of cyanide, which gave 2 : 3-dihydroxy-6 : 7-dimethoxynaphtha-1 : 4-quinone-5-carboxylic acid (IV; R = OMe). This reaction of phthalaldehydes, to give *iso*naphthazarin derivatives, was developed by Weygand and his collaborators (*Ber.*, 1942, **75**, 625; 1943, **76**, 818; *Chem. Ber.*, 1947, **80**, 391). The preparation of the corresponding *iso*naphthazarin derivative (IV; R = Me) from gladiolic acid has been carried out independently (Weygand, Weber, and Grove, *Chem. and Ind.*, 1954, 106).

Experimental

Ultra-violet absorption spectra were determined in ethanol solution unless otherwise stated.

Gladiolic Acid Hydrate Triacetate.—Deoxygladiolic acid (300 mg.) (Brown and Newbold, *J.*, 1953, 3648) and sodium metaperiodate (3·0 g.) in N-sulphuric acid (20 c.c.) were refluxed for 40 hr. The cooled solution, which deposited crystals, was extracted with chloroform (3 × 25 c.c.), and the combined extracts were washed with water (20 c.c.), aqueous sodium hydrogen carbonate (3 × 20 c.c.; 10%), and water (20 c.c.) and dried (Na_2SO_4). Evaporation of the chloroform and crystallisation of the residue from benzene–light petroleum (b. p. 60—80°) gave deoxygladiolic acid (220 mg.) as needles, m. p. and mixed m. p. 173—174°. The combined sodium hydrogen carbonate extracts were acidified (Congo-red) with 3N-hydrochloric acid and extracted with chloroform (3 × 25 c.c.), and the combined chloroform extracts were washed with water (20 c.c.) and dried (Na_2SO_4). Evaporation of the chloroform gave a pale yellow solid (50 mg.) which gave a strong positive test for gladiolic acid (Grove, *Biochem. J.*, 1952, **50**, 648) with ammonia. The solid was heated on the steam-bath for 10 min. with acetic anhydride (2 c.c.) and sulphuric acid (1 drop; *d* 1·84), and the solution poured on crushed ice (5 g.); an oil separated, rapidly solidifying. This was extracted with chloroform (3 × 15 c.c.), the combined extracts were washed with aqueous sodium hydrogen carbonate (2 × 10 c.c.; 10%) (combined to give solution A) and with water (10 c.c.), dried (Na_2SO_4), and evaporated. Crystallisation of the residue from aqueous ethanol gave gladiolic acid hydrate triacetate (12 mg.) as needles, m. p. 131—132° undepressed on admixture with a specimen prepared from natural gladiolic acid (Found: C, 55·4; H, 5·1. Calc. for $C_{17}H_{18}O_9$: C, 55·7; H, 4·95%). Light absorption: Max. at 2140 (ε 37,000) and 2980 (ε 3100), inflexion at 2340 Å (ε 7000).

Gladiolic Acid.—The triacetate (19 mg.) was heated under reflux for 1 hr. with 2N-sulphuric acid (2·5 c.c.). The gladiolic acid which crystallised from the cooled solution recrystallised

from water as needles (11 mg.), m. p. 159—160° alone or mixed with a specimen of natural gladiolic acid kindly supplied by Mr. J. F. Grove (Found : C, 59·7; H, 4·8. Calc. for $C_{11}H_{10}O_5$: C, 59·5; H, 4·5%). Light absorption : Max. at 2140 (ε 18,500), 2710 (ε 6900) and 3040 Å (ε 3200). The 2 : 4-dinitrophenylhydrazone separated from glacial acetic acid as orange needles, m. p. and mixed m. p. 231—233° (decomp.).

iso*Gladiolic Acid*.—Solution A from the triacetate formation was acidified (Congo-red) with 3N-hydrochloric acid, and the solution extracted with chloroform (3 × 10 c.c.). The extracts were washed with water (10 c.c.) and dried (Na_2SO_4). Evaporation, and crystallisation of the resulting solid from aqueous ethanol, gave *iso*gladiolic acid (33 mg.) as needles, m. p. and mixed m. p. 232—233° (Found : C, 59·8; H, 4·8. Calc. for $C_{11}H_{10}O_5$: C, 59·5; H, 4·5%). Light absorption : Max. at 2180 (ε 33,000) and 3000 (ε 4400) and inflexion at 2450 Å (ε 8600).

3-*Formylopianic Acid*.—4-Formylmeconin (140 mg.) (Brown and Newbold, *loc. cit.*) was heated under reflux for 3 hr. with a solution of sodium metaperiodate (1·5 g.) in N-sulphuric acid (10 c.c.). The cooled solution was extracted with chloroform (3 × 15 c.c.), the combined extracts were washed with aqueous sodium hydrogen carbonate (2 × 10 c.c.; 10%) and water (10 c.c.), dried (Na_2SO_4), and evaporated, and the residue crystallised from methanol to give 4-formylmeconin (100 mg.) as blades, m. p. and mixed m. p. 193—195°. The combined aqueous washings were acidified (Congo-red) with 3N-hydrochloric acid and extracted with chloroform (3 × 20 c.c.). Evaporation of the dried (Na_2SO_4) chloroform extracts followed by crystallisation of the residue from water gave 3-formylopianic acid (17 mg.) as fine needles, m. p. 173—174° undepressed on admixture with a specimen prepared by Brown and Newbold (*J.*, 1952, 4878) (Found : C, 55·6; H, 4·5. Calc. for $C_{11}H_{10}O_6$: C, 55·5; H, 4·2%). Light absorption : Max. at 2110 (ε 21,000), 2750 (ε 4400) and 3190 Å (ε 3900). The pK_a value, 5·1, which we gave for this acid (*loc. cit.*) was determined in 50% aqueous ethanol; in water it has pK_a 4·3.

2 : 3-*Dihydroxy*-6 : 7-*dimethoxynaphtha*-1 : 4-*quinone*-5-*carboxylic Acid* (with J. Blair).—A mixture of 3-formylopianic acid (250 mg.), glyoxal sodium bisulphite (300 mg.), and potassium cyanide (50 mg.) was treated with 2N-sodium carbonate (7 c.c.), and the mixture kept for 1 hr. at room temperature with frequent shaking and free access of air. The deep purple solution was made acid (Congo-red) with 3N-hydrochloric acid, and the red solution kept at 0° for 2 days. 2 : 3-*Dihydroxy*-6 : 7-*dimethoxynaphtha*-1 : 4-*quinone*-5-*carboxylic acid* which separated crystallised from water as small red needles (100 mg.), m. p. 249—253° (decomp.) (Found, after drying at 110° for 5 hr. : C, 53·0; H, 3·7. $C_{13}H_{10}O_8$ requires C, 53·1; H, 3·4%). The compound is very soluble in methanol and ethanol, slightly soluble in ether, benzene, and chloroform, and insoluble in light petroleum. It dissolves in aqueous sodium hydroxide giving a blue solution, and in aqueous sodium hydrogen carbonate with effervescence to give a violet solution. Light absorption : in H_2O, max. at 2700 (ε 13,600), 2940 (ε 5700) and 4400 Å (ε 280); in 0·05N-NaOH, max. at 2160 (ε 34,000) and 5450 (ε 370), inflexion at 2450—2500 Å (ε 12,000).

We are indebted to Professor F. S. Spring, F.R.S., for constant encouragement, to Mr. J. F. Grove for helpful co-operation, and to Mr. John Blair, B.Sc., for carrying out the experiment indicated. One of us (J. J. B.) thanks the Governors of The Royal Technical College for the award of the Nobel Scholarship. Gifts of chemicals from Messrs. T. & H. Smith, Ltd., and Imperial Chemical Industries Limited, Dyestuffs Division, are gratefully acknowledged. The microanalyses were by Mr. Wm. McCorkindale, and the ultra-violet absorption spectra were measured by Miss Sheila Mackenzie.

The Royal Technical College, Glasgow. [*Received, December 16th*, 1953.]

Organometallic Compounds of the Alkali Metals. Part III. Metallation of Alkylbenzenes by Alkyl-sodium and -potassium Compounds. The Character of Aromatic Metallation Reactions.*

By D. Bryce-Smith.

[Reprint Order No. 4773.]

The metallation of toluene, ethylbenzene, *iso*propylbenzene, and *tert.*-butylbenzene has been investigated by an extension of the procedure described in Part II.* The tendency for reaction at the α-position of the side chain decreases in the order, toluene > ethylbenzene > *iso*propylbenzene. Isomer ratios have been determined for the metallation of *iso*propylbenzene by ethylpotassium, *n*-amylpotassium, and *n*-amylsodium: the *meta*-isomer has always predominated. Competition experiments have shown that the *iso*propyl and the *tert.*-butyl group act as deactivating substituents towards nuclear metallation. Partial rate factors have been determined for the metallation of *iso*propylbenzene. The results are considered to show that the rate-determining step in this type of reaction is a nucleophilic attack on hydrogen by the anion of the reagent: the substitution is termed "protophilic." The partial rate factors are regarded as a measure of the relative acidities of the corresponding hydrogen atoms.

Schorigin (*Ber.*, 1910, **43**, 1938) described the metallation of toluene, ethylbenzene, xylenes, and mesitylene by ethylsodium, and observed that the α-position in the side chain was a favoured point of attack. Gilman and his co-workers (*J. Amer. Chem. Soc.*, 1940, **62**, 1514; 1946, **68**, 522), using a method similar to Schorigin's, found that ethyl-sodium and -potassium attack at the α-position in *iso*propylbenzene, although the possibility of nuclear substitution was not excluded in the latter case. Morton, Massengale, and Brown (*ibid.*, 1945, **67**, 1620) reported that *n*-amylsodium attacks *iso*propylbenzene "largely *para* and some *ortho* to the *iso*propyl group." Morton and Little subsequently (*ibid.*, 1949, **71**, 487) described further metallation experiments, using a mixture of *n*-amylsodium and sodium *iso*propoxide, said to be more reactive than *n*-amylsodium alone. The mixed reagent was reported to attack principally the *para*-positions of *iso*propyl- and *tert.*-butyl-benzene.

The present paper deals with an extension to alkylbenzenes of the metallation procedure described in Part II (*loc. cit.*), whereby alkylpotassium compounds are produced *in situ* by the action of potassium upon the corresponding alkyl-lithium compounds. Information upon three main points has been sought: (*a*) the connection between the nature of the alkyl group in an alkylbenzene and the degree of metallation at the α-position by a particular reagent; (*b*) the effects of variations in reagent and temperature on the metallation of a particular alkylbenzene; (*c*) the effect of alkyl substituents on nuclear metallation. For investigation of (*a*), ethylpotassium has been used since it leads to negligible dimetallation (cf. Part II, *loc. cit.*). For (*b*), the metallation of *iso*propylbenzene has proved most convenient since, with this hydrocarbon, substitution occurs largely in the nucleus, and the isomer ratios may be easily determined by a chemical method. In this method, one portion of the mixture of isomeric monocarboxylic acids which results from carboxylation of the arylpotassium compounds is oxidised by chromium trioxide in acetic acid. This converts αα-dimethylphenylacetic acid into benzoic acid, and *m*- and *p*-*iso*propylbenzoic acids into a mixture of *iso*phthalic and terephthalic acids. The phthalic acids are separated *via* the dithallous salts (Bryce-Smith, *Chem. and Ind.*, 1953, 244). Oxidation of another portion of the acids by alkaline permanganate converts the *iso*propylbenzoic acids into the water-soluble 2-(carboxyphenyl)propan-2-ols but leaves unchanged any αα-dimethylphenylacetic acid. The proportion of *o*-*iso*propylbenzoic acid is obtained by difference, for no method of direct estimation has been found. All attempts to detect the presence of β-phenylbutyric acid by oxidation experiments have failed, and in view of the relatively aliphatic character of β-positions in alkylbenzenes the possibility of β-metallation has been neglected.

* Part II, *J.*, 1953, 861.

The accuracy of this method of analysis has been judged by experiments with synthetic mixtures, and small corrections have been applied where necessary.

Experimental

Purification of Materials.—Benzene and *n*-pentane were purified as in Part II (*loc. cit.*). Toluene was sulphur-free material which was further purified by fractional distillation over sodium through a column of approx. 10 theoretical plates. Ethylbenzene was shaken repeatedly with portions of concentrated sulphuric acid until the acid layer was only slightly coloured, then washed, dried, and fractionated over sodium. *iso*Propylbenzene was a gift from the Anglo-Iranian Oil Co. Ltd., which is gratefully acknowledged : it was of 99·86 mole % purity and had f. p. −96·036°. *tert.*-Butylbenzene was prepared by Kharasch and Brown's method (*J. Amer. Chem. Soc.*, 1939, **61**, 2142) and purified as for ethylbenzene. All materials were thoroughly dried.

The general procedure for metallation by alkylpotassium compounds described in Part II (*loc. cit.*) has been used without modification in the present work.

(a) *Metallation of Toluene by Ethylpotassium.*—A solution of ethyl-lithium (0·138 mole) in toluene (120 ml.) was stirred with an alloy of potassium (6·6 g., 0·17 g.-atom) and sodium (1·5 g.). Evolution of ethane commenced within a few minutes at 20°, and after 84 hr. the reaction was 90% complete (titration of aliquot portions of the clear supernatant liquid obtained by sedimentation). After treatment with solid carbon dioxide in ether, phenylacetic acid (4·3 g.) was obtained, having m. p. and mixed m. p. 76·5° without recrystallisation. Evaporation of an ethereal extract of the mother-liquors gave a further 0·35 g. of almost pure acid, m. p. 74—75°. No other aromatic acids could have been present in significant amounts.

In view of the fact that some tolyl metallic compounds can rearrange to the corresponding benzyl isomers (Bachmann and Clarke, *J. Amer. Chem. Soc.*, 1927, **49**, 2089 ; Gilman *et al.*, *ibid.*, 1940, **62**, 673, 1514), it was clearly desirable to demonstrate the absence of such rearrangement under the conditions of experiment (*a*). This was done as follows.

(b) *Preparation and Attempted Rearrangement of* p-*Tolylpotassium.*—A solution of *p*-tolyl-lithium was prepared by the reaction of *p*-bromotoluene (17·1 g., 0·1 mole) with lithium (1·5 g., 0·215 g.-atom) in ether (75 ml.); the yield was 95%. Ether was removed under reduced pressure with stirring, and the residue was heated at 60° for 30 min. under reduced pressure. Benzene (45 ml.) was added, and then an alloy of potassium (7·8 g., 0·2 g.-atom) and sodium (2 g.). The mixture was stirred at 20° for 10 hr. and then kept overnight. By filtration of a portion of the dark brown product and titration of the filtrate, the reaction was found to be essentially complete. A further amount of benzene (150 ml.) was added and the suspension of *p*-tolylpotassium was kept at 20° for 40 days with occasional shaking (nitrogen atmosphere). Reaction with solid carbon dioxide then afforded 8·4 g. of impure *p*-toluic acid, m. p. 155—158°. Recrystallisation from water gave the pure acid, m. p. 179°, together with a little impure benzoic acid, m. p. 112—114° and mixed m. p. 115—116°, of which further recrystallisation did not raise the m. p. Phenylacetic acid was not obtained, and its characteristic odour was not in evidence.

In another experiment, a suspension of *p*-tolylpotassium in benzene was heated at 78° for 45 min. before carboxylation. *p*-Toluic acid was obtained, but no trace of benzoic or phenylacetic acid.

Since benzylpotassium is stable under the conditions of the above experiments, no rearrangement of the *p*-tolylpotassium could have occurred.

(c) *Metallation of Ethylbenzene by Ethylpotassium.*—To ethyl-lithium (0·117 mole) and ethylbenzene (65 ml.) was added an alloy of potassium (7·5 g., 0·19 g.-atom) and sodium (1·7 g.). After the mixture had been stirred for 66 hr. at an average temperature of 20°, the reaction was 89% complete. After carboxylation of the bright red product there were obtained 4·7 g. (27%) of a mixture of isomeric monocarboxylic acids, b. p. 264—270° : no dicarboxylic acids were found, but propionic acid (0·5 g.) was isolated. No 2 : 3-dimethylbutane or other neutral reaction products were detected. 1·0 g. of the mixture of acids was converted into the mixed amides in the usual manner. Repeated recrystallisation, first from water and then from light petroleum, gave hydratropamide (0·15 g.), m. p. 90—91°. Janssen (*Annalen*, 1889, **250**, 136) reported m. p. 91—92°.

Oxidation experiments. (i) A solution of 0·98 g. of the mixture of acids in water (60 ml.) and sodium hydroxide (3 ml. of 10% solution) was oxidised at 100° by potassium permanganate (3·5 g.), added during 20 min.; excess of permanganate remained after a further 40 min. at 100°. The solution was decolorised by sulphur dioxide and, while warm, was filtered from insoluble

acids (0·13 g.). The filtrate was saturated with salt and extracted with chloroform to give benzoic acid (0·35 g.), m. p. and mixed m. p. 121°. From the combined mother-liquors there was obtained a trace of material, m. p. 60—100° (very indefinite) : the presence in this of phthalic acid was shown by a strongly positive " phenolphthalein test." The insoluble *iso*- and tere-phthalic acids were converted into the dimethyl esters, and these were separated from each other by the method described in Part II (*loc. cit.*). The proportion was approx. 60% of *iso*- and 40% of tere-phthalic acid. Identities of the esters were confirmed by mixed m. p. determinations.

(ii) 1·08 g. of the original mixture of acids in glacial acetic acid (14 ml.) were oxidised at 100° by the gradual addition of chromium trioxide (5·5 g. of dry " AnalaR "). After 3 hr., water (40 ml.) and concentrated sulphuric acid (10 ml.) were added and the mixture was heated under reflux for 9 hr. more. A slight excess of oxidising agent remained. By this means there were obtained benzoic acid (0·45 g., 51%), m. p. and mixed m. p. 120—121°, and a mixture of *iso*- and terephthalic acids (0·27 g., 23%) in the proportion of approx. 60 : 40 respectively, *i.e.*, the same as in (i).

(iii) 1·06 g. of the original mixture of acids in glacial acetic acid (7 ml.) were oxidised at 80° by chromium trioxide (0·6 g.), and the mixture was heated at 100° for 4 hr. and then kept at room temperature for 14 days. The acetic acid was neutralised by addition of sodium hydroxide solution at 0—10° and there was added a solution of sodium hypobromite prepared from bromine (2 ml.) and sodium hydroxide (4·0 g.) in water (30 ml.). The mixture was kept at 0° for 30 hr. and then warmed at 70° for a further 2 hr. A mixture of *iso*- and tere-phthalic acids (0·12 g., 10%) was obtained; estimation *via* the thallous salts (Bryce-Smith, *loc. cit.*) showed that the respective proportions were 64 and 36%.

The fact that the ratio of *iso*- to tere-phthalic acid was largely independent of the method of oxidation suggests that this ratio is an approximate measure of the relative amounts of *m*- and *p*-ethylbenzoic acids present in the original mixture.

(d) *Metallation of* iso*Propylbenzene by Ethylpotassium at* 20°.—To ethyl-lithium (0·115 mole) and *iso*propylbenzene (65 ml.) was added an alloy of potassium (9 g., 0·23 g.-atom) and sodium 1·8 g.). The mixture was stirred for 8 days, by which time the evolution of ethane had almost ceased, and was then poured on solid carbon dioxide and ether. Free alkali metals were destroyed, as always, by addition of aqueous *tert.*-butyl alcohol. The acidified product was extracted with light petroleum (b. p. 40—60°; 2 × 50 ml.), a trace of insoluble material being removed by filtration. Distillation of the dried (Na_2SO_4) extract gave a forerun of propionic acid (0·4 g.); the bulk (5·85 g.) distilled at 145—152°/5 mm., and partly crystallised on long storage; *ca.* 0·1 g. of colourless crystalline dicarboxylic acids remained in the distillation flask. The main fraction was a mixture of αα-dimethylphenylacetic acid and *iso*propylbenzoic acids : the isomeric composition was determined by the following two experiments, the conditions of which will be subsequently referred to as the " standard conditions."

(i) *Oxidation by chromium trioxide.* To 1·5282 g. of the homogeneous mixture of acids in boiling glacial acetic acid (21 ml.) was added dry " AnalaR " chromium trioxide (8·2 g.) in very small portions during 30 min. The mixture was kept at 130° (bath-temp.) for 24 hr. with occasional shaking and was then boiled under reflux for 30 min. with water (80 ml.) and concentrated sulphuric acid (27 ml.). The insoluble phthalic acids were filtered off at 20°, and washed with a little water and then with 2 ml. each of cold glacial acetic acid and chloroform; the yield was 1·1054 g. (71·3%). 0·2827 g. of these acids gave 0·3961 g. (40·6%) of thallous terephthalate and 0·1675 g. (59·2%) of *iso*phthalic acid; a duplicate estimation gave 40·1 and 59·5%, respectively.

The efficiency of the above process was tested by performing the oxidation under similar conditions of a synthetic mixture (60 : 40) of *m*-* and *p*-*iso*propylbenzoic acids, whereby 87·5% of the *meta*-isomer appeared as *iso*phthalic acid and 98·6% of the *para*-isomer as thallous terephthalate; a duplicate estimation gave 87·0 and 97·6% respectively. Corrections have been applied on the basis of these results.

(ii) *Oxidation by permanganate.* 1·6972 g. of the mixture of acids were dissolved in a solution of sodium hydroxide (1·2 g.) in water (75 ml.), and the solution was heated with potassium permanganate (5·1 g.) for 4 hr. at 100°. The solution was decolorised by passage of sulphur dioxide and then further acidified by hydrochloric acid. The crystals were filtered off. The filtrate was extracted twice with light petroleum (b. p. 40—60°), and the extract was itself extracted with 10 ml. of 10% sodium hydroxide solution. Acidification gave a further small quantity of solid acid, which was combined with the first crop. The acid obtained at this stage was almost pure αα-dimethylphenylacetic acid, but contained a little *iso*- and tere-phthalic acids. The crystals were washed with chloroform–light petroleum until there was no further loss in weight. The total loss was 0·2016 g. (11·9%) and represented the weight of αα-dimethyl-

* The writer is indebted to Dr. F. H. C. Stewart for supplying a specimen of this acid.

phenylacetic acid which had been present. Evaporation of the washings gave this acid, which was pure without recrystallisation (m. p. and mixed m. p. 79°). Ziegler and Schnell (*Annalen*, 1924, **437**, 255) recorded m. p. 77—78°. A checking experiment showed that the acid is slightly attacked by alkaline permanganate under the above conditions. Account being taken of this, the corrected proportion of αα-dimethylphenylacetic acid in the original mixture was 13%.

The aqueous liquors from the permanganate oxidation contained 2(carboxyphenyl)propan-2-ols and furnished a mixture of *iso*- and tere-phthalic acids when further oxidised by potassium dichromate and sulphuric acid. The yield was slightly lower than in the direct oxidation by chromium trioxide.

(e) *Metallation of* iso*Propylbenzene by Ethylpotassium at* 85°.—An experiment similar to (*d*) was performed with similar quantities, except that sodium was omitted. The mixture was stirred at 90° for 30 min. to initiate a reaction with the potassium and was then kept at 85° for a further 30 min. Separation of a brown putty-like solid prevented stirring beyond this period. A gas, presumably ethane, was evolved during the reaction, but no gas was evolved at 90° before the addition of potassium : this showed that ethyl-lithium does not metallate *iso*propylbenzene under these conditions. Carboxylation and the subsequent operations were carried out as described in (*d*). 3·5 g. of a liquid mixture of monocarboxylic acids were obtained. Dimetallation was negligible. Oxidation of 1·0300 g. of the acids with chromium trioxide under the standard conditions gave 0·6611 g. (63·5%) of a mixture of *iso*- and tere-phthalic acids. Estimation *via* the thallous salts gave 60·6, 61·0% of *iso*phthalic acid and 39·1, 38·6% of terephthalic acid. Oxidation of 1·2260 g. of the original mixture of acids with alkaline permanganate under the standard conditions gave 0·2090 g. (17·0%) of αα-dimethylphenylacetic acid, m. p. 78·5°. This acid did not form a *p*-bromophenacyl ester under the usual conditions. Neutral products from the metallation reaction were examined. 2 g. of a liquid (which contained much *iso*propylbenzene), b. p. 154—210°, were oxidised by chromium trioxide in glacial acetic acid. Benzoic acid was obtained, but no more than a trace of *iso*- and tere-phthalic acids. Had ethyl*iso*propylbenzenes been present (cf. Part II, *loc. cit.*), only the *ortho*-isomer would have escaped detection by this method. No 2 : 3-dimethyl-2 : 3-diphenylbutane was found.

(f) *Metallation of* iso*Propylbenzene by* n-*Amylpotassium at* 20°.—A solution of *n*-amyl-lithium (0·142 mole) in *iso*propylbenzene (65 ml.) was stirred with an alloy of potassium (11 g., 0·28 g.-atom) and sodium (2·2 g.) for 7 days. No gas was evolved and the dark brown solid product did not settle, so the progress of the reaction could not be followed by the usual methods. Distillation of the mixture of acids which was obtained after carboxylation gave fractions with the following b. p.s at 8 mm. : (i) 120—140° (4·1 g.), (ii) 140—150° (0·3 g.), (iii) 150—165° (8·5 g.), (iv) residue > 165° (*ca.* 0·2 g.). Fraction (i) was hexanoic acid; (iii) was the required mixture of isomeric monocarboxylic acids; (iv) crystallised during the final stages of distillation and was almost certainly a mixture of *iso*propylphthalic acids. Oxidation of 1·6126 g. of the liquid fraction (iii) with chromium trioxide under the standard conditions gave 1·1586 g. (71·0%) of a mixture of *iso*- and tere-phthalic acids : a duplicate oxidation gave 70·6%. Estimation *via* the thallous salts gave 55·7, 56·0, 55·1% of *iso*- and 44·0, 43·7, 44·5% of tere-phthalic acid. Oxidation of 1·5034 g. of fraction (iii) with alkaline permanganate under the standard conditions gave 0·1776 g. (11·8%) of αα-dimethylphenylacetic acid, m. p. 78·5°.

(g) *Metallation of* iso*Propylbenzene by* n-*Propylpotassium at* 90°.—A solution of *n*-propyl-lithium (0·107 mole) in *iso*propylbenzene (90 ml.) was stirred at 90° for 4 hr. with potassium (8·2 g., 0·21 g.-atom). A portion of the evolved gas was condensed in a trap cooled in liquid air, and found to be an approx. 4 : 1 mixture of propane and propene. Carboxylation of the organometallic product gave 4·5 g. of a mixture of monocarboxylic acids, b. p. 140—145°/4 mm., together with 0·5 g. of dicarboxylic acids. Oxidation of 1·547 g. of the monocarboxylic acids with alkaline permanganate under the standard conditions gave 0·270 g. (17·5%) of αα-dimethylphenylacetic acid, m. p. 77—78°. This experiment was performed before a satisfactory means of estimating the nuclear isomers had been found, and reliable figures for these are therefore not available. Some rather crude initial experiments indicated that the proportions of nuclear isomers were of the same order as those subsequently found in experiment (e). No alkylation products or 2 : 3-dimethyl-2 : 3-diphenylbutane was detected.

(h) *Metallation of* iso*Propylbenzene by* n-*Amylsodium at* 20°.—A suspension of *n*-amylsodium was prepared by the addition (2½ hr.) of a solution of *n*-amyl chloride (16 g., 0·15 mole : Eastman-Kodak material shaken with concentrated sulphuric acid, washed, and refractionated; b. p. 106—108°) in *n*-pentane (50 ml.) to sodium (11·5 g., 0·5 g.-atom : wire of 0·5 mm. diam.) in *n*-pentane (100 ml.). The temperature was kept at −10° to −15° and the mixture was vigorously stirred. The usual conditions for the exclusion of air and moisture were observed.

After a further ½ hour's stirring at 0°, the mixture was kept overnight at −50°. *n*-Pentane was removed by distillation at reduced pressure and *iso*propylbenzene (70 ml.) was then added. The mixture was stirred at an average temperature of 20° for 10 days, and was then poured on solid carbon dioxide and ether. Distillation of the resulting acids gave, after a small forerun of hexanoic acid (0·75 g.), the required mixture of aromatic monocarboxylic acids (8·45 g.), b. p. 160—170°/9 mm. A yellow-brown gum (0·5 g.) remained as distillation residue, but there was no apparent formation of dicarboxylic acids. The main fraction solidified on cooling and was homogenised by melting before samples were taken for analysis. Oxidation of 1·6341 g. of the acids with chromium trioxide under the standard conditions gave 1·4623 g. (88·5%) of a mixture of *iso*- and tere-phthalic acids. Estimation *via* the thallous salts gave 48·5% of *iso*phthalic acid and 51·3, 51·5% of terephthalic acid. Dimethyl *iso*phthalate had m. p. 63° and mixed m. p. 66° (pure 67°); dimethyl terephthalate had m. p. and mixed m. p. 141·5° The acids (2·1300 g.) were oxidised under the standard conditions by potassium permanganate except that a higher proportion (7 g.) was used. There was isolated αα-dimethylphenylacetic acid (0·0136 g., 0·7%), m. p. and mixed m. p. 78° without recrystallisation. Practically no neutral reaction products were found. A neutral liquid (0·2 g.), b. p. *ca.* 270°, may have been impure *n*-amyl-*iso*propylbenzene (Found: C, 88·3; H, 10·25. Calc. for $C_{14}H_{22}$: C, 88·4; H, 11·6%).

(i) *Metallation of* tert.-*Butylbenzene by Ethylpotassium at* 85°.—A solution of ethyl-lithium (0·114 mole) in *tert.*-butylbenzene (70 ml.) was stirred at 95° with potassium (8·5 g., 0·22 g.-atom) until reaction commenced (30 min.), and was then cooled to 85°. After 40 min., the solids agglutinated into a putty-like mass and stirring became impossible. Gas evolution continued for a further 2 hr. at 85°. Carboxylation was effected in the usual manner, the lumps of solid potassium compound being cautiously broken up by means of a spatula. Mono- and di-carboxylic acids were separated on the basis of the latters' virtual insolubility in light petroleum (b. p. 40—60°). The dicarboxylic acids (1·7 g.) had m. p. 315—325°. The *tert.*-butylbenzoic acids were freed from propionic acid and remaining traces of dicarboxylic acids through a silica gel column, methylene dichloride being the eluant (yield, 6·05 g.) (Found: C, 74·0; H, 7·85. Calc. for $C_{11}H_{14}O_2$: C, 74·1; H, 7·9%).

Crawford and Stewart (*J.*, 1953, 288) recorded the following solubilities (g./100 g.) for the copper salts of *tert.*-butylbenzoic acids in benzene–ethanol (9 : 1) at 25°: *para* 0, *meta* 4·8, *ortho* 35. This suggested a method for determining the proportion of the *para*-isomer in a mixture. Also, the copper salt of the *ortho*-acid appears to be much more soluble in ethanol than is the salt of the *meta*-acid. A separation was attempted on this basis. 0·9050 G. of the homogeneous mixture of acids gave 1·0810 g. of copper salts (102% as $C_{22}H_{26}O_4Cu$). The salts were heated under reflux with 26 ml. of benzene–ethanol (9 : 1), and the mixture cooled to 25° and filtered to give 0·3771 g. (35·5% as $C_{22}H_{26}O_4Cu$) of insoluble salt: this gave 0·2787 g. (30·9%) of *p-tert.*-butylbenzoic acid, m. p. 163°, which after recrystallisation from aqueous ethanol had m. p. 164·5°. Attempts to obtain the pure *meta*-acid (m. p. 127°) failed. All the crops of acids had m. p. >85°, which made improbable the presence of any considerable amounts of *o-tert.*-butylbenzoic acid, m. p. 68·5°, or β-methyl-β-phenylbutyric acid, m. p. 59°: the latter acid would result from β-metallation. The copper salts were all hygroscopic and appeared to be readily solvated. With allowance for probable losses, the proportion of the *para*-isomer is put at 35—40%. No satisfactory method for oxidising the *tert.*-butylbenzoic acids to phthalic acids has been found.

(j) *Competitive Metallation of Benzene and* iso*Propylbenzene by Ethylpotassium.*—A solution of ethyl-lithium (0·19 mole) in benzene (46·8 g., 0·6 mole) and *iso*propylbenzene (72·0 g., 0·6 mole) was stirred with potassium (14·8 g., 0·38 g.-atom) at 85° for 4¾ hr. Refluxing did not occur. It was found that 99% of the ethyl-lithium had been consumed. After carboxylation there were obtained 8·0 g. of a first crop of solid acids. The aqueous liquors were saturated with salt and extracted twice with light petroleum. The first crop of acids was heated with glacial acetic acid (35 ml.), cooled, and filtered. The insoluble residue was further treated with acetic acid (20 ml.) (yield, 1·55 g.). [This material was a mixture of *iso*- and tere-phthalic acids, the ratio of which has already been quoted in Part II (*loc. cit.*).] The combined acetic acid filtrates were diluted with water (100 ml.) and extracted four times with light petroleum (b. p. 40—60°) to obtain all the solid monocarboxylic acids. Finally, repeated ether-extraction gave 0·25 g. of a high-melting solid, assumed to be a mixture of *iso*propylphthalic acids. The combined light petroleum extracts were fractionated to remove solvent, and the colourless solid residue was kept under reduced pressure over potassium hydroxide and paraffin wax until there was no further loss in weight. The relative proportions of benzoic and cuminic acids in the mixture (6·2 g.) were determined as follows. 2·3748 g. of the acids in glacial acetic acid (15 ml.)

were oxidised at 130° by gradual addition of chromium trioxide (5·5 g.). The mixture was kept at 130° for 23 hr. and was worked up in the usual manner to furnish 0·4649 g. of a mixture of *iso*- and tere-phthalic acids, equivalent to 0·732 g. (31%) of total cuminic acids (cf. Expt. e) (Found, for the original mixture of acids : C, 69·9; H, 5·75. Calc. for a mixture containing 69% $C_7H_6O_2$ and 31% $C_{10}H_{12}O_2$: C, 70·2; H, 5·7%). The aqueous liquors from the oxidation experiment furnished benzoic acid (1·5 g.), m. p. 120° (an estimated 0·05 g. of this was derived from the oxidation of αα-dimethylphenylacetic acid). The *iso*- and tere-phthalic acids were separated *via* the thallous salts : *iso*- 61·6, tere- 37·9, 37·7%. These percentages are within 1% of those found from the metallation of *iso*propylbenzene in the absence of benzene (Expt. e). The slight dimetallation which occurred was taken into account when the total rate factor was calculated, but no correction was applied for the slight change in the proportions of benzene and *iso*propylbenzene during the course of the metallation reaction. The corrected proportions by weight were : cuminic acids 27·5, benzoic acid 72·5%.

The total rate factor, $F^{C_6H_5Pr^i}_{C_6H_6} = 0{\cdot}28(3)$.
The total rate factor for nuclear metallation = 0·23.

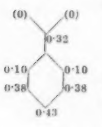
(k) *Competitive Metallation of Benzene and* tert.*-Butylbenzene by Ethylpotassium.*—A solution of ethyl-lithium (0·19 mole) in benzene (46·8 g., 0·6 mole) and *tert.*-butylbenzene (80·5 g., 0·6 mole) was stirred with potassium (14·8., 0·38 g.-atom) at 85° for 3 hr. Refluxing did not occur. Carboxylation gave 9·7 g. of a mixture of colourless solid acids. *iso*- and Tere-phthalic acids (1·98 g.) were removed as in the previous experiment. There was also obtained 0·30 g. of a solid, m. p. 285—295°, assumed to be a mixture of *tert.*-butylphthalic acids. The solid monocarboxylic acids were freed from propionic acid and traces of dicarboxylic acids by passage of a solution in light petroleum through a column of silica gel (yield, 6·8 g.) (Found : C, 69·65; H, 5·55% ; equiv., 135·2, 135·5. Calc. for a mixture containing 76·5% $C_7H_6O_2$ and 23·5% $C_{11}H_{14}O_2$: C, 70·05; H, 5·65% ; equiv., 135·2). In calculation of the total rate factor, the slight dimetallation was taken into account :

$$F^{C_6H_5Bu^t}_{C_6H_6} = 0{\cdot}19.$$

The proportion of *para*-substitution in *tert.*-butylbenzene being taken as 35% (Expt. i), the corresponding partial rate factor is 0·4.

Discussion

The principal results of this work may be summarised as follows. (*a*) The *iso*propyl and the *tert.*-butyl group deactivate all positions in the aromatic nucleus towards metallation by ethylpotassium : the total rate factors for nuclear substitution in *iso*propylbenzene and *tert.*-butylbenzene are 0·23 and 0·19, respectively. With the former group (and probably with the latter also), the order of increasing deactivation is *para* < *meta* < *ortho*, as is shown by the partial rate factors for *iso*propylbenzene (I).



(I)

(*b*) Orientation in the metallation of *iso*propylbenzene appears not to be influenced greatly by the size of the alkyl group in the reagent, but more by the nature of the metal : in comparison with potassium, sodium leads to somewhat increased *para*-substitution at the expense of *ortho*- and α-substitution.

(*c*) Metallation at the α-positions in toluene, ethylbenzene, and *iso*propylbenzene forms the following proportions of the total substitution in these compounds : toluene, 100% ; ethylbenzene, 50% ; *iso*propylbenzene, 13%.

(*d*) Ratios of isomers vary slightly with the reaction temperature, as shown below :

Ratios of isomers (%) *in the metallation of* iso*propylbenzene.*

Reagent	Temp.	α	*ortho*	*meta*	*para*	Reagent	Temp.	α	*ortho*	*meta*	*para*
C_2H_5K	20°	13·0	9·0	48·5	29·5	*n*-$C_5H_{11}K$	20°	13·0	9·5	45·5	32·0
C_2H_5K	85	19·0	11·5	44·5	25·0	*n*-$C_5H_{11}Na$	20	1·0	3·0	49·5	46·5
n-C_3H_7K ...	90	19·0	14 *	43 *	24 *						

* Approximate value.

The yields of acids from metallation experiments are generally not quantitative, but this fact does not complicate interpretation of the present data. Beyond the products indicated, no neutral or acid derivatives of the aromatic hydrocarbon have been detected.

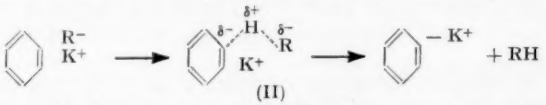
The side reaction seems to be an innocuous thermal decomposition of the alkylpotassium compound which, if analogous to the decomposition of alkyl-lithium compounds, will proceed mainly, *e.g.*, as follows: $C_2H_5K \longrightarrow C_2H_4 + KH$ (Ziegler and Gellert, *Annalen*, 1950, **567**, 179: cf. Carothers and Coffman, *J. Amer. Chem. Soc.*, 1930, **52**, 1254).

Several mechanisms for aromatic metallation reactions have been advanced, but none has yet been established behond doubt. Thus, Morton and his co-workers (*Chem. Reviews*, 1944, **35**, 1; *J. Amer. Chem. Soc.*, 1945, **67**, 1620; 1949, **71**, 487) have regarded the reactions as electrophilic in nature. This view appeared to be supported by evidence that the *iso*propyl group is an *ortho–para*-directing substituent. Some 50% of *meta*-substitution has now been observed in the metallation of *iso*propylbenzene by *n*-amylsodium: it seems probable that the acid, m. p. 47—49°, isolated by Morton *et al.* (*loc. cit.*) from such an experiment was *m-iso*propylbenzoic acid (m. p. 50°), and not the *ortho*-isomer as claimed. In some of these workers' later experiments, sodium *iso*propoxide was present, and it seems possible, albeit unlikely, that this compound influences the orientation. Roberts and Curtin (*ibid.*, 1946, **68**, 1658), on the basis of experiments using alkyl-lithium compounds, suggested that metallation involves a nucleophilic attack on hydrogen by the anion of the reagent; but this view was not accepted by Morton (*ibid.*, 1947, **69**, 969). Klapproth and Westheimer (*ibid.*, 1950, **72**, 4461) demonstrated that aromatic mercuration can show either electrophilic or homolytic characteristics, depending upon the experimental conditions. There is some doubt whether much more than a formal analogy can be drawn between mercuration and the present metallation reactions; *e.g.*, the substitution patterns in toluene are totally different.

In attempting to interpret the present results, it is assumed that alkyl- and aryl-potassium compounds are polar, and function as undissociated ion-pairs: this seems to follow from their physical properties. (For discussions of the evidence relevant to structure, see Morton, *Chem. Reviews*, 1944, **35**, 1; Sidgwick, "The Chemical Elements and their Compounds," Oxford, pp. 81, 100; Coates, *Quart. Reviews*, 1950, **4**, 217.) Possible rate-determining steps for metallation by alkylpotassium compounds appear to be limited to the following: (*a*) an electrophilic attack on carbon by the cation of the reagent; (*b*) a nucleophilic attack on hydrogen by the anion of the reagent; (*c*) the formation of a tetrapolar transition state involving the simultaneous operation of (*a*) and (*b*) in various degrees of relative importance; (*d*) the addition of RK to the nucleus, followed by loss of RH: and there is the final possibility that the reaction is homolytic. Several of these mechanisms can be excluded. An electrophilic attack by the metal cation (Morton *et al.*, *locc. cit.*) can be reconciled neither with the extensive *meta*-substitution which occurs in *iso*propylbenzene, nor with the fact that alkyl groups—electron donors—behave as deactivating substituents. Furthermore, if both reagent, RK, and product, ArK, are regarded as ion-pairs, the dominant rôle in the reaction can scarcely be attributed to the metal cation, since this emerges with little or no change in its electronic configuration. These considerations likewise exclude any "push-pull" mechanism of type (*c*) where the electrophilic attack is energetically the more important. The main objection to an addition–elimination reaction of type (*d*), apart from the reluctance of benzene to undergo addition reactions, is that in cases where addition does occur (*e.g.*, the addition of alkyl–lithium compounds to pyridine), it is always followed by loss of the metal hydride. Alkylsodium compounds metallate olefins, $R{\cdot}CH{:}CH_2$, mainly at the α-position (Morton and Holden, *J. Amer. Chem. Soc.*, 1947, **69**, 1675): this would not be expected if the first step were one of addition to the double bond. A homolytic mechanism (which need not involve attack by *free* radicals) can also be excluded with fair certainty, although the published data suitable for comparison are rather sparse. Dannley and Zaremsky (Amer. Chem. Soc. Meeting, Sept., 1953) have reported that the homolytic phenylation of *iso*propylbenzene (which probably does not involve the abstraction of a hydrogen atom in the rate-determining stage) leads to the following proportions of attack at the nuclear positions: *ortho*, 10; *meta*, 60; *para*, 30%. These are very similar to the present metallation ratios; but the similarity does not extend to total (and hence, partial) rate factors. The total rate factors for the phenylation of *iso*propyl- and *tert.*-butyl-benzene are 2·1 and 0·75 respectively (Cadogan, Hey, Pengilly, and Williams, personal communication), whereas the correspond-

ing figures for metallation are 0·28 and 0·19. Such differences in the relative reaction rates are considered to imply basically different mechanisms, and the similarity in isomer ratios is thought to be fortuitous. This belief is reinforced by Dannley and Zaremsky's observation (*loc. cit.*) that only slight α-phenylation of toluene occurs, substitution being mainly in the nucleus. Gregg and Mayo (*Discuss. Faraday Soc.*, 1947, **2**, 328) have shown that the ease of abstraction of a hydrogen atom from the α-position in alkylbenzenes is much greater than from the nucleus in benzene and alkylbenzenes, and increases in the order toluene < ethylbenzene < *iso*propylbenzene. α-Metallation follows the reverse order, and the rate of metallation at a position in benzene is some three times as great as at the α-position in *iso*propylbenzene.* It follows that the rate-determining step in both side-chain and nuclear metallation is not the abstraction of a hydrogen atom. This receives negative support from the present failure to detect dimers of benzyl-type radicals among the reaction products. An electron-transfer mechanism, which would involve the formation of alkyl radicals and, in consequence, of benzyl-type radicals, is also clearly improbable.

The possibilities remaining are either a nucleophilic attack on hydrogen (Roberts and Curtin, *loc. cit.*; cf. Bradley and Jadhav, *J.*, 1948, 1622) or a " push-pull " mechanism in which such attack is energetically the more important. Both are consistent with the present results, but the conception of reagent and substitution product as ion-pairs suggests a tetrapolar transition state of the type pictured in (II). In this picture, the function of



(II)

the metal cation is purely electrostatic, the motive force for the reaction arising from the difference in energies between the alkyl and aryl carbanions. Doubtless, the field of the reagent will act to magnify the incipient polarisation of the C–H bond, the positive field of the cation facilitating withdrawal of the proton : to this extent, the cation may be said to participate. In order to describe substitution reactions which involve the abstraction of a proton in the rate-determining stage, it seems appropriate to revive the term " protophilic," at one time used synonymously with " nucleophilic." Such reactions are not " nucleophilic substitutions " in the usual sense, for the aromatic nucleus retains the electrons of the original C–H bond : a nucleophilic substitution involving RK would require attack on *carbon* by R^-, with expulsion of a hydride ion and the formation of an alkylbenzene; indeed, this occasionally seems to happen (Part II, *loc. cit.*).

The protophilic viewpoint requires that reaction should be more hindered than helped by any effect which causes the accession of electrons to the site of substitution. This accords with the observed deactivating effect of alkyl substituents in metallation. Moreover, Shoppee (*J.*, 1930, 968; 1931, 1225; 1932, 696) has found that the introduction of alkyl substituents retards prototropic rearrangement reactions. It is a feature of the transition state (II) that feasible alternative pentadienate structures cannot be drawn : the nucleus loses no electrons, and its resonance should not be appreciably disturbed (in contrast with current views on the mechanism of electrophilic and nucleophilic aromatic substitution). Therefore, inductive effects should be of more importance than electromeric upon the transition state, as pointed out by Roberts and Curtin (*loc. cit.*). Suppose we express the perturbation transmitted to nuclear positions by an alkyl substituent as inversely proportional to the corresponding partial rate factors. The perturbation ratio *ortho* : *meta* : *para* in the metallation of *iso*propylbenzene by ethylpotassium is then 10 : 2·65 : 2·3. For saturated carbon chains, it has been assumed by several workers (*e.g.*, Dewar, *J.*, 1949, 463; Gold, *Trans. Faraday Soc.*, 1950, **46**, 109; following Derick, *J. Amer. Chem. Soc.*, 1911, **33**, 1181) that the transmitted inductive effects of substituents are proportional to $1/3^n$, where n is the number of carbon atoms traversed. Application of this to the case of

* In the absence of data from competition experiments, it might be argued that the decreasing tendency for α-metallation in this series could be due equally well to increasing nuclear activation as to decreasing activation of the α-positions. The α-position in toluene must be the most reactive, for it is attacked readily by phenylsodium, for example, under conditions where the other hydrocarbons are inert.

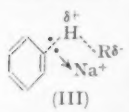
a substituent in benzene gives a ratio, 10 : 3·65 : 2·2, for the magnitudes of inductive influences transmitted to *ortho-*, *meta-*, *and para*-positions respectively : it is assumed that the effect reaches each position additively by two routes. If an inverse-square law were obeyed, the corresponding ratio would be 10 : 3·0 : 2·15. Whatever the precise distance relationship may be in aromatic compounds, it appears that the observed perturbation ratios are of the order expected from the prevailing operation of inductive effects. This, of course, neglects the influence of steric factors on the rate of substitution at *ortho*-positions : such factors may perhaps be of small account in the metallation of *iso*propylbenzene, since the proportion of *ortho*-metallation is the same with ethylpotassium as with the rather more bulky *n*-amylpotassium. The close similarity of the isomer ratios in these two cases eliminates the possibility of any appreciably selective effect on collision frequencies arising from the non-coincidence of the centres of charge and mass in the reagents.

The ease of α-metallation, decreasing in the order toluene > ethylbenzene > *iso*propylbenzene, follows the order of decreasing electron recession from the side chain to the nucleus by the hyperconjugation effect. This recession would favour a protophilic attack at the α-position. Admittedly, hyperconjugation is a mesomeric, rather than an inductive, effect; but α-metallation presents a special case, for the charge on the resulting benzyl anion (unlike that on a nuclear anion) may be de-localised by resonance. It is noteworthy that the release of a proton from a C–H bond appears to be aided by arylation at the carbon atom and hindered by alkylation, whereas the release of a hydrogen atom is aided by both (Gregg and Mayo, *loc. cit.*).

It is clear from the foregoing discussion that the rate of metallation at a given position must be related to the acidity of the hydrogen which is replaced (cf. the acidity series of Conant and Wheland, *ibid.*, 1932, **54**, 1212, and McEwen, *ibid.*, 1936, **58**, 1124). Application of the Brønsted relationship to transition states of the type $\left[\overset{\delta-}{\text{Et}}\cdots\overset{\delta+}{\text{H}}\cdots\overset{\delta-}{\text{Ar}}\right]\text{K}^+$ gives the equation $\log_{10}(k/k') = \alpha(\text{p}K' - \text{p}K)$ where k and k' are the rates of metallation at two similar positions. The factor α is less than unity, and is a measure of the degree of unit charge on hydrogen in the transition state. Since the value of this is unknown, the equation cannot be applied quantitatively at present. Qualitatively, the equation indicates that each hydrogen atom in *iso*propylbenzene is less acidic than a hydrogen atom in benzene, the order of decreasing acidity being *para* > *meta* > α > *ortho* (>β). The values of 10^5K at 25° for *p*- and *m-iso*propylbenzoic acid (personal communication from Mr. F. W. Laxton, Chelsea Polytechnic) are 4·43 and 5·4 respectively, compared with 6·3 for benzoic acid (*ortho*-alkylbenzoic acids are abnormally strong, owing to steric factors which seem unlikely to intervene significantly in *ortho*-metallation; cf Dippy, *Chem. Reviews*, 1939, **25**, 151). Thus, in metallation, the deactivation of *meta*- and *para*-positions by the *iso*propyl group accords with the effect of this group on the strengths of the corresponding carboxylic acids, but the relative effects on *meta*- and *para*-positions are reversed. Closer similarity is perhaps not to be expected. It should be noted that the acidity relationship will not generally apply to metallation reactions of the type discussed by Roberts and Curtin (*loc. cit.*), where loose co-ordination occurs between the reagent and the attacked species. The predominance of *ortho*-substitution in such cases is probably more an expression of steric facilitation than of any inherent reactivity of the *ortho*-positions.

Some modification of the above conclusions appears to be necessary in the case of metallation by alkylsodium compounds. So far, experimental difficulties have militated against the use of *n*-amylsodium in competition experiments, but comparison of the isomer ratios for the metallation of *iso*propylbenzene by *n*-amylsodium and by *n*-amylpotassium shows the former reagent slightly to favour substitution at the negative end of the hydrocarbon molecule. This apparent trend towards electrophilic behaviour is not great, but is thought to be significant. It might be explained as follows. The efficiency of nuclear screening in alkali-metal cations decreases with decreasing atomic weight. To this cause may probably be traced the marked covalent character of organolithium compounds, and their evident ability loosely to co-ordinate with certain compounds containing unshared electrons, particularly ethers : the failure of benzylpotassium to metallate dibenzofuran under conditions where benzylsodium is effective (Gilman *et al.*, *J. Amer. Chem. Soc.*, 1941,

63, 2479) suggests, however, that organopotassium compounds have little tendency to co-ordinate. Thus, in passing from potassium to sodium, electron shifts illustrated in (III) may begin to make a finite reduction in the overall energy of the transition state; *i.e.*, electrophilic attack by the metal cation may assume a greater relative importance. Alternatively, the effect may be one of loose co-ordination of the metal with the aromatic π-electrons (such as can occur in the case of certain silver salts), thus causing slight localisation of the reagent at the more negative regions of the hydrocarbon. If some such explanation is correct, we may expect the *trend* towards electrophilic behaviour to be more noticeable in organolithium compounds; and even electrophilic mercuration may yet take its place in a general pattern.



(III)

Investigation of the mechanism of aromatic metallation is being continued.

The author thanks Dr. V. Gold for discussions. This work has been carried out during the tenure of an I.C.I. Research Fellowship at the University of London.

KING'S COLLEGE, LONDON, W.C.2. [*Received, November 6th*, 1953.]

The Chemistry of Polymerised Oils. Part IV. Thermal Polymerisation of Some Long-chain Unsaturated Fatty Esters.*

By A. L. CLINGMAN, D. E. A. RIVETT, and DONALD A. SUTTON.

[Reprint Order No. 4778.]

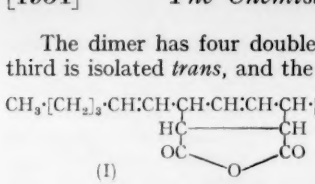
A formal structural proof is given that addition of the Diels–Alder type takes place during thermal dimerisation of methyl β-elæostearate. The method employed has also been applied to the thermal dimers of some unconjugated unsaturated fatty esters.

THERE has been strong but indirect evidence for many years (Bradley, *J. Oil Colour Chem. Assoc.*, 1947, **30**, 225) that both conjugated and unconjugated unsaturated long-chain fatty esters dimerise when heated, to give Diels–Alder type adducts. Farmer and Morrison-Jones (*J.*, 1940, 1339) (cf. Wheeler, *J. Amer. Chem. Soc.*, 1948, **70**, 3467) isolated from the total dimer mixture of methyl sorbate relatively small percentages of crystalline *cyclo*hexene derivatives whose structures proved that Diels–Alder reaction had occurred. The thermal dimer from unconjugated pentadiene was shown by Ahmad and Farmer (*J.*, 1940, 1176) to be a complex mixture containing *cyclo*hexenes from which phthalic acid was isolated in unstated (presumably small) yield by a dehydrogenation–oxidation sequence. Boelhouwer, Jol, and Waterman (*Research*, 1952, **5**, 336) used their method of ring analysis on the dimers from a variety of long-chain unsaturated fatty esters and showed that rings were present. However, the total available evidence does not prove that the bulk of the dimer molecules from the common long-chain unsaturated esters have, in fact, the required six-membered ring substituted in four neighbouring positions.

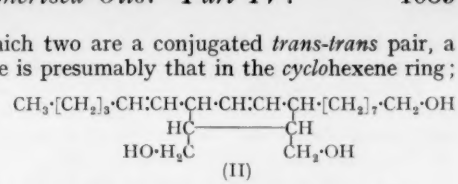
As has already been reported in brief (*Chem. and Ind.*, 1953, 798), the dimer of methyl β-elæostearate, on substitutive bromination followed by dehydrobromination and then oxidation, gave prehnitic acid (benzene-1 : 2 : 3 : 4-tetracarboxylic acid) in 9% overall molar yield, thus demonstrating the presence of a six-membered ring substituted in four neighbouring positions, as required by the Diels–Alder hypothesis. It is most unlikely that cyclisation occurred during the dehydrobrominations since pure prehnitic acid, free from pyromellitic acid, was invariably obtained. The yield of prehnitic acid obtained from (I) (Morrell and Samuels, *J.*, 1932, 2251) by the substitutive bromination–dehydrobromination–oxidation sequence was 35% and from the corresponding trialcohol (II) it was 13%. The latter was used as a model, in addition to (I), to take account of possible effects on the yield of prehnitic acid caused by the direct attachment of the anhydride group to the ring.

* Part III, Matic and Sutton (*J.*, 1952, 2679).

The dimer has four double bonds, of which two are a conjugated *trans-trans* pair, a third is isolated *trans*, and the remaining one is presumably that in the *cyclo*hexene ring;

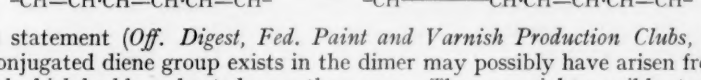


(I)

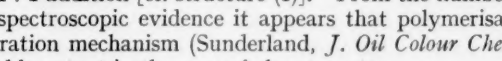


(II)

these considerations conform with expectations since β-elæostearic acid is the all-*trans*-form of octadeca-9 : 11 : 13-trienoic acid (Paschke, Tolberg, and Wheeler, *J. Amer. Oil Chem. Soc.*, 1953, **30**, 97). The polymerisation therefore occurs as follows:



Wheeler's statement (*Off. Digest, Fed. Paint and Varnish Production Clubs*, 1951, 661) that no conjugated diene group exists in the dimer may possibly have arisen from the use of material which had been heated more than ours. There are eight possible stereoisomeric forms of the dimer; this number is reduced to four if only the 9th and 12th carbon atoms are involved in the 1 : 4-addition [cf. structure (I)]. From the number of double bonds in the dimer and the spectroscopic evidence it appears that polymerisation does not occur by a hydrogen-separation mechanism (Sunderland, *J. Oil Colour Chem. Assoc.*, 1945, **28**, 137) to any appreciable extent in the case of elæostearate.



Prehnitic acid has also been obtained from the dimer of methyl linoleate (*ca.* 3% yield), the dimer of methyl linolenate (*ca.* 2% yield), and from the dimeric fraction from the polymerisation of a sunflower seed oil (*ca.* 4% yield); the latter was included to provide an example from a triglyceride oil polymerisation. The yield of prehnitic acid is greatly dependent upon the proportion of *N*-bromosuccinimide used; details are in the Experimental section.

The yields of prehnitic acid obtained from the dimers of the unconjugated unsaturated esters used are considerably less than from methyl β-elæostearate dimer. This comparison may indicate that Diels–Alder type addition is not the sole operative mechanism in the case of the unconjugated esters. Alternatively, the severe heat treatment necessarily applied to these materials during dimer formation may have caused alteration to the structures first formed, with a resultant lowering of the yield of prehnitic acid.

Experimental

Preparation and Properties of Methyl β-Elæostearate Dimer.—Methyl β-elæostearate ($E^{1\%}_{1\,cm.}$ 1850 at 268 mμ) (41·5 g.) was sealed in an evacuated Pyrex bulb and heated at 185° for 4·5 hr. After removal of residual monomer by repeated passages through a falling-film molecular still at 105°, the dimer (5·5 g.) was distilled off at 205°. This dimer fraction [Found: C, 77·9; H, 11·0%; *M* (ebullioscopic in benzene), 582. Calc. for $(C_{19}H_{32}O_2)_2$: C, 78·0; H, 11·0%; *M*, 585] had n_D^{30} 1·490 and $E^{1\%}_{1\,cm.}$ 527 at 234 mμ. It had bands in the infra-red at 985 and 965 cm.$^{-1}$ characteristic of *trans-trans*-conjugated unsaturation and isolated *trans*-unsaturation respectively (Jackson, Paschke, Tolberg, Boyd, and Wheeler, *J. Amer. Oil Chem. Soc.*, 1952, **29**, 229). There was no band at 948 cm.$^{-1}$ characteristic of *cis-trans*-conjugated unsaturation (*idem, loc. cit.*). On hydrogenation (Adams platinum catalyst in acetic acid) four mols. of hydrogen were taken up; the product, an oil, gave no colour with tetranitromethane.

Preparation of Methyl Linoleate Dimer.—Methyl linoleate (*Org. Synth.*, 1942, **22**, 75) (60 g.) was heated in a sealed evacuated bulb at 295—300° for 12 hr. Residual monomer was removed by repeated passages through a falling-film molecular still at 105° and the dimer (23 g.) was distilled off at 205°.

Preparation of Methyl Linolenate Dimer.—Methyl linolenate (*Org. Synth.*, 1942, **22**, 82) was heated as above at 295—300° for 4·5 hr. and the dimer separated by molecular distillation.

Preparation of Dimer from Sunflower Seed Oil.—Commercial (propane-segregated) sunflower seed oil (Marine Oil Refiners of Africa, Ltd., containing *ca.* 67% of combined linoleic acid) was

kept at 295—300° for 13 hr. in a sealed evacuated flask. After saponification and esterification with methanol, the dimeric esters were separated as above.

Preparation of the Trialcohol (II).—This *alcohol* was prepared by lithium aluminium hydride reduction of the product from the Diels–Alder reaction between methyl β-elæostearate and maleic anhydride. A mixture of methyl β-elæostearate (45·7 g.) and maleic anhydride (15·3 g.) was stirred under nitrogen at 85—90° for 0·75 hr. and the product crystallised from benzene–pentane, to yield needles, m. p. 61—62° (9·5 g., 16%) (Found: C, 70·8; H, 8·9. $C_{23}H_{34}O_5$ requires C, 70·7; H, 8·8%). This ester was also obtained (21% overall yield) on esterification with diazomethane in ether of the maleic anhydride–β-elæostearic acid adduct (I).

A solution of the ester, m. p. 61—62° (3·1 g.), in dry ether (50 c.c.) was added during 0·5 hr. with stirring to lithium aluminium hydride (1·5 g.) in ether (50 c.c.) and refluxed for a further 2 hr. The complex was decomposed with dilute sulphuric acid and the *product* extracted with ether. Since it crystallised with difficulty, it was again treated with lithium aluminium hydride, and the product crystallised from ether, to give needles (2·1 g., 75%), m. p. 75—76°, raised on recrystallisation to 77—78° (Found: C, 75·4; H, 11·6. $C_{22}H_{40}O_3$ requires C, 75·0; H, 11·45%).

Dehydrogenation–Oxidation Experiments.—(1) *The maleic anhydride adduct* (I) *of* β-*elæostearic acid.* The adduct (Morrell and Samuels, *loc. cit.*; Rinkes, *Rec. Trav. chim.*, 1943, **62**, 557) (2 g.) and *N*-bromosuccinimide (4·7 g., 5 mols.) in carbon tetrachloride (30 c.c.) were refluxed for 3·5 hr. After being kept overnight, the precipitated succinimide (2·5 g.; theor. 2·6 g.) was filtered off and the filtrate evaporated. The residue was heated under nitrogen at 120° for 1 hr. with *NN*-diethylaniline (5 c.c.). Water (100 c.c.) containing potassium hydroxide (2 g.) was added and the mixture gently refluxed during the slow addition of powdered potassium permanganate (50 g.). After 24—30 hours' heating the excess of permanganate was destroyed by the addition of a little ethanol. The hot solution was filtered and the solid filter-cake extracted twice with hot water. The combined filtrates were acidified with hydrochloric acid, concentrated by distillation, and extracted with ether continuously for 24 hr. in an efficient liquid–liquid extractor. The extracted solid was dissolved in methanol–ether, and an excess of diazomethane in ether added. After evaporation of the solvent, the residue was heated at 80°/0·5 mm. for 0·5 hr. to remove methyl oxalate, and then crystallised from methanol, to give tetramethyl prehnitate (0·58 g., 35%), m. p. and mixed m. p. 130—131°, raised to 132—133° on recrystallisation (Found: C, 54·5; H, 4·7. Calc. for $C_{14}H_{14}O_8$: C, 54·2; H, 4·55%).

(2) *The trialcohol* (II). A solution of the trialcohol (0·83 g.) and *N*-bromosuccinimide (3·35 g., 8 mols.) in carbon tetrachloride (35 c.c.) was refluxed for 10 hr. and then kept overnight. After the precipitated succinimide (2·0 g., theory 1·9 g.) had been filtered off, the filtrate was evaporated and treated first with *NN*-diethylaniline (2·5 c.c.) and then with potassium permanganate (65 g.) as in (1), to give finally tetramethyl prehnitate (0·095 g., 13%). Treatment of the trialcohol with 7 and with 10 mols. of *N*-bromosuccinimide gave 7% and 10% yields, respectively, of prehnitate.

(3) *The dimer of methyl* β-*elæostearate.* A solution of the dimer (2·00 g.) and *N*-bromosuccinimide (4·88 g., 8 mols.) in carbon tetrachloride (40 c.c.) was refluxed for 8 hr. and then kept overnight. The filtrate after removal of the precipitated succinimide (2·7 g.; theor. 2·7 g.) was evaporated and treated with *NN*-diethylaniline (4 c.c.) and potassium permanganate (95 g.) as in (1), to give finally tetramethyl prehnitate (0·093 g., 9%). With 6 mols. of *N*-bromosuccinimide the yield of prehnitate was 6%.

(4) *The dimers of methyl linoleate and methyl linolenate, and that from sunflower seed oil.* These were treated in 3-g. quantities with various amounts of *N*-bromosuccinimide as in (3) above. The highest yields of tetramethyl prehnitate obtained with the molar proportion of *N*-bromosuccinimide stated in parentheses were: methyl linoleate (7), 3%; methyl linolenate (7), 2%; sunflower seed oil (6), 4%.

Early unsuccessful attempts to dehydrogenate the systems studied by catalytic methods were made by one of us (D. A. S.) in collaboration with R. N. J. Barraclough and A. F. Sherwood at the Paint Research Station, Teddington. This paper is published by permission of the South African Council for Scientific and Industrial Research.

National Chemical Research Laboratory,
South African Council for Scientific and Industrial Research,
Pretoria. [*Received, November 9th*, 1953.]

The Preparation of Thorium Alkoxides.

By D. C. Bradley, M. A. Saad, and W. Wardlaw.

[Reprint Order No. 4873.]

By means of reactions involving thorium tetrachloride alcoholates $ThCl_4,4ROH$ or pyridinium thorium hexachloride $(C_5H_6)_2ThCl_6$ with ammonia or sodium alkoxides, thorium tetra-alkoxides $Th(OR)_4$ (R = Me, Et or Pr^i) have been prepared. They are complex, non-volatile, and alkaline. These properties are discussed from the theoretical standpoint.

Recent work on the structural chemistry of the alkoxides of Group IVA elements (Bradley, Mehrotra, and Wardlaw, *J.*, 1952, 4204) suggested that thorium alkoxides should possess some interesting properties. These appear not to have been prepared hitherto.

Experience with titanium, zirconium, and hafnium suggested the following possible methods for preparing thorium alkoxides :

$$Th + 4ROH \longrightarrow Th(OR)_4 + 2H_2 \quad . . . . . (a)$$

$$ThCl_4 + 4ROH + 4NH_3 \longrightarrow Th(OR)_4 + 4NH_4Cl \quad . . . . . (b)$$

$$ThCl_4 + 4NaOR \longrightarrow Th(OR)_4 + 4NaCl \quad . . . . . (c)$$

$$(C_5H_6N)_2ThCl_6 + 6NH_3 + 4ROH \longrightarrow Th(OR)_4 + 6NH_4Cl + 2C_5H_5N \quad . . . . (d)$$

$$(C_5H_6N)_2ThCl_6 + 6NaOR \longrightarrow Th(OR)_4 + 6NaCl + 2ROH + 2C_5H_5N \quad . (e)$$

It was not possible to realise method (*a*) although several substances, *e.g.*, $HgCl_2$, I_2, $Zr(OEt)_4$, $CH_3{\cdot}COCl$, etc., were tried as catalysts. This failure of thorium to react is interesting in comparison with the behaviour of other metallic elements with alcohols. Thus it is well-known that the alkali metals, magnesium, and aluminium react vigorously with the lower alcohols although for magnesium and aluminium catalysts are required.

The other methods met with various degrees of success. When ammonia was used [methods (*b*) and (*d*)] the resulting thorium compounds contained appreciable percentages of chloride whereas the products from methods (*c*) and (*e*) were chloride-free. This behaviour was readily understood when it was found that alcoholic solutions of thorium ethoxide or thorium *iso*propoxide were alkaline to thymolphthalein. On the other hand anhydrous ammoniacal alcohol was acidic to this indicator. Thus thorium alkoxides are more basic than ammonia and the following equilibria are feasible :

$$Th(OR)_4 + NH_4^+ \rightleftharpoons Th(OR)_3^+ + NH_3 + ROH \quad . . . . . (i)$$

$$Cl^- + Th(OR)_3^+ \rightleftharpoons Th(OR)_3Cl \quad . . . . . (ii)$$

Ammonium chloride is appreciably soluble in ammoniacal alcohol and thus affords the ions required to favour the products on the right-hand sides of (i) and (ii). There is little doubt that the complete replacement of chloride effected by sodium alkoxides is caused by the low solubility of sodium chloride in alcohols.

The best results were obtained with method (*c*) involving the reaction between $ThCl_4,4Pr^iOH$ and sodium *iso*propoxide. Thorium tetra*iso*propoxide was a white solid, very soluble in *iso*propyl alcohol or benzene, and sublimed at 200—210°/0·05—0·1 mm. It was instantly hydrolysed, even by traces of water. Ebullioscopic measurements in benzene and in *iso*propyl alcohol gave molecular complexities of 3·8 and 1·8 respectively. The high complexity in benzene was not surprising in view of the low volatility of thorium *iso*propoxide. Moreover, zirconium *iso*propoxide (b. p. 160°/0·1 mm.) is trimeric in benzene and stereochemical considerations would predict a lower volatility and higher complexity for thorium *iso*propoxide. The lower complexity in *iso*propyl alcohol can be attributed to the " donor " nature of the solvent and the greater ionic dissociation of thorium *iso*propoxide in this solvent. The latter possibility is being investigated conductometrically.

Preliminary experiments on the preparation of thorium ethoxide by the methods (*b*), (*d*), and (*e*) gave a benzene-soluble product which was not the pure ethoxide. It contained

chlorine and products of hydrolysis. Later work employing improved means of avoiding hydrolysis showed that pure thorium ethoxide was only sparingly soluble in benzene or ethyl alcohol. In one experiment most of the thorium ethoxide was co-precipitated with sodium chloride and was less hydrolysed than the thorium ethoxide remaining in solution. Consequently these methods are unsuitable for preparing thorium ethoxide, and the pure compound was obtained from the *iso*propoxide by alcohol interchange: $Th(OPr^i)_4 + 4EtOH \longrightarrow Th(OEt)_4 + 4Pr^iOH$.

The ethoxide was so sparingly soluble in benzene or ethyl alcohol as to preclude the determination of its molecular weight. It is interesting that the solubility of zirconium ethoxide in benzene is also very sensitive to impurity, and in the same sense. The pure zirconium compound is transformed by fusion into a soluble form which reverts to the insoluble form after crystallisation from benzene; but pure thorium tetraethoxide has no melting point and no soluble form was obtained.

Thorium tetramethoxide, a white insoluble powder [like $Zr(OMe)_4$], was prepared from the *iso*propoxide by alcohol interchange. Neither the tetramethoxide nor the tetraethoxide of thorium could be sublimed below 300° at 0·05 mm. and above this temperature pyrolysis occurred.

Unlike titanium and zirconium, thorium derivatives do not form complex lower alkoxides with sodium alkoxides. Moreover, the stability of the sodium zirconium alkoxides appears to be much greater than that for the titanium derivatives, as judged by the behaviour of the metal tetrachlorides with sodium alkoxides: titanium tetraalkoxides are thus obtained, yet the addition of exactly four equivalents of sodium ethoxide to one mole of zirconium tetrachloride gives no zirconium tetraethoxide but, instead, a complex sodium zirconium ethoxide. The behaviour of thorium tetrachloride with sodium alkoxide resembles that of titanium tetrachloride. For example, thorium *iso*propoxide is readily obtained by the reaction: $ThCl_4 + 4NaOPr^i \longrightarrow Th(OPr^i)_4 + 4NaCl$. Addition of sodium *iso*propoxide (1 equiv.) to thorium *iso*propoxide (1 mol.) gave no crystalline sodium–thorium complex, and thorium *iso*propoxide was recovered by sublimation under reduced pressure. The tendency of the lower alkoxides of titanium, zirconium, and thorium to combine with sodium alkoxides appears to be in the order $Ti < Zr \gg Th$. The different behaviour of titanium and zirconium alkoxides may be due to a combination of steric and electronic effects, but the contrast between the derivatives of zirconium and thorium is presumably a result of electronic factors alone. Thus zirconium appears to be comparatively electrophilic because zirconium alkoxides are acidic towards thymolphthalein and can be titrated to a sharp end-point with sodium alkoxides. However, although thorium alkoxides are complex substances and probably involve thorium in either 6 or 8 co-ordination with oxygen, it is clear that the electropositive nature of the thorium atom predominates because the alkoxides are definitely alkaline towards thymolphthalein and do not appear to form compounds with sodium alkoxides.

Experimental

Apparatus.—All-glass apparatus of the type previously described (*loc. cit.*) was used. For the addition of sodium *iso*propoxide, which is sparingly soluble in *iso*propyl alcohol, to the thorium halides a Soxhlet apparatus proved most satisfactory. Exceptional precautions were necessary to avoid hydrolysis of the new compounds, for once hydrolysis had occurred none of the substances described below could be purified by crystallisation or sublimation. Air or nitrogen admitted to an apparatus was dried first with silica gel and finally with phosphoric oxide. " Portex " tubing was used in place of rubber tubing for the connection of the phosphoric oxide tube to the apparatus.

Materials.—The preparation of pyridinium thorium hexachloride and the alcoholates of thorium chloride will be described in another communication.

Very dry ethyl alcohol (water content *ca.* 0·003%) was prepared from " absolute " alcohol by first drying it azeotropically with benzene and then adding sodium ethoxide and diethyl phthalate.

" AnalaR " *iso*propyl alcohol was dried (to water content *ca.* 0·007%) by the azeotropic method in a fractionating column (120 cm.) packed with Fenske glass helices.

Methyl alcohol was dried by refluxing it with freshly prepared magnesium methoxide.

Ammonia gas from a cylinder was dried over freshly ignited quicklime.

Analytical Methods.—Thorium was determined by precipitating thorium hydroxide and igniting this to the dioxide. The alkoxide radicals were determined by the volumetric method previously described (*loc. cit.*).

Preparation of Thorium Ethoxide.—(1) *From thorium tetrachloride tetraethyl alcoholate.* A solution of the alcoholate $ThCl_4$,4EtOH (20·35 g.) in ethyl alcohol (33 g.) and benzene (45 g.) was treated with excess of ammonia. After completion of the exothermic reaction the free ammonia was removed under reduced pressure and the ammonium chloride by filtration. The filtrate was evaporated to dryness under reduced pressure and gave impure thorium tetraethoxide as a white solid (12·75 g.) [Found: Th, 57·6; OEt, 40·8; Cl, 1·6. Calc. for $Th(OEt)_4$: Th, 56·3; OEt, 43·7%].

(2) *From pyridinium thorium hexachloride.* The complex thorium chloride $(C_5H_6N)_2ThCl_6$ (15·9 g.) was suspended in ethyl alcohol (72 g.) and benzene (50 g.) and treated with excess of ammonia. After filtration, evaporation of the filtrate gave a white solid (8·37 g.) with a high chloride content (Found: Th, 58·2; OEt, 32·3; Cl, 8·3%).

In another experiment involving the complex thorium chloride (6·42 g.), ethyl alcohol (34 g.), benzene (45·5 g.), and excess of ammonia the filtrate obtained after the removal of ammonium chloride was evaporated to half-bulk and re-treated with ammonia. The final filtrate gave on evaporation to dryness a white solid (3·3 g.) with a lower chloride content (Found: Th, 56·6; OEt, 39·5; Cl, 2·5%).

In an attempt to obtain chloride-free thorium ethoxide the product (6·97 g.) containing 8·3% of Cl was dissolved in ethyl alcohol (70 g.) and treated with sufficient sodium ethoxide [from sodium (0·38 g.) in the Soxhlet apparatus] to combine with all the chloride. After filtration, a small quantity (1·4 g.) of solid was obtained by evaporation of the filtrate (Found: Th, 57·4; OEt, 38·1; Cl, 0·9%). The precipitate was a mixture of sodium chloride and thorium ethoxide, the latter being less hydrolysed (EtO : Th = 3·98 : 1) than the material (EtO : Th = 3·43 : 1) obtained from the filtrate.

(3) *From thorium tetra*iso*propoxide.* Thorium tetra*iso*propoxide (5·03 g.) was treated with boiling ethyl alcohol (160 g.) for 4 hr. A solid (2·8 g.) was obtained by filtration (Found: Th, 56·7; OEt, 42·6%). This was initially soluble in benzene but after one day had become insoluble in benzene or ethyl alcohol. The suspension in ethyl alcohol was alkaline to thymolphthalein.

Preparation of Thorium iso*Propoxide.*—(1) *Methods involving the use of ammonia.* (*a*) The alcoholate $ThCl_4$,4Pr^{i}OH (18·5 g.), suspended in *iso*propyl alcohol (43 g.) and benzene (200 g.), was treated with excess of ammonia. When reaction had ceased, free ammonia was removed under reduced pressure and the ammonium chloride filtered off. The filtrate was evaporated and left a highly viscous solid (12·23 g.) which was dried at 80° under reduced pressure [Found: Th, 51·3; OPr^i, 47·6; Cl, 2·2. Calc. for $Th(OPr^i)_4$: Th, 49·5; OPr^i, 50·5%].

At 0·1 mm. this product (0·67 g.) softened at 80° and sublimed at 200—210°. A white crystalline sublimate (0·29 g.) was obtained (Found: Th, 50·4; OPr^i, 49·0; Cl, 0·7%). Further sublimation did not improve the purity.

(*b*) The complex chloride $(C_5H_6N)_2ThCl_6$ (12 g.), suspended in *iso*propyl alcohol (71 g.) and benzene (52 g.), was treated with excess of ammonia. After the removal of ammonium chloride by filtration the filtrate was evaporated to dryness under reduced pressure and gave a white solid (5·8 g.) (Found: Th, 52·8; OPr^i, 38·9; Cl, 7·0%). An attempt was made to lower the chloride content of this product by treatment with sodium *iso*propoxide. The foregoing product (4·9 g.) in boiling *iso*propyl alcohol (80 g.) was allowed to react with sodium *iso*propoxide produced from sodium (0·23 g.) in the Soxhlet extractor. The finely divided precipitate was removed by filtration through a sintered glass (No. 4) filter supporting a pad of "Hyflo-Supercel." The filtrate was evaporated to dryness under reduced pressure and gave a white solid (3·2 g.) (Found: Th, 50·7; OPr^i, 47·9; Cl, 0%).

(2) *Methods involving sodium* iso*propoxide.* (*a*) The complex pyridinium chloride (7·19 g.), suspended in *iso*propyl alcohol (60 g.), was heated in the boiler of a Soxhlet extractor, while sodium (1·62 g.) was in a sintered glass bucket in the extraction compartment. After about ½ hr. the solutions in the boiler and in the extraction chamber had become yellow, probably owing to reaction between pyridine and metallic sodium. The brown solid (4·9 g.) obtained after the removal of sodium chloride and evaporation of solvent was chloride-free (Found: Th, 51·2%).

(*b*) The method from thorium tetrachloride tetra*iso*propyl alcoholate was most satisfactory for the preparation of pure thorium tetra*iso*propoxide and many experiments were conducted

with a view to finding the optimum conditions. The following exemplifies the final method. The alcoholate (35·9 g.) in *iso*propyl alcohol (280 g.) was caused to react with the sodium *iso*propoxide produced by combination of sodium (5·36 g.) in a Soxhlet apparatus (as above) with the boiling alcohol. A white solid (24·4 g., 89%) remained after the removal of sodium chloride and solvent in the usual way (Found: Th, 49·6; OPr^i, 50·2%). Thorium tetra*iso*propoxide appeared to melt at 110° under reduced pressure and a white crystalline sublimate was obtained at 200°/0·05 mm. The compound readily dissolved in *iso*propyl alcohol or benzene and in the former solvent it was alkaline to phenolphthalein and to thymolphthalein.

Molecular weights were determined ebullioscopically in both solvents, with the apparatus and methods previously described (*loc. cit.*) [Found: *M*, in benzene, 1760, in *iso*propyl alcohol, 861. $Th(OPr^i)_4$ requires *M*, 468]. The results were independent of concentration up to *ca.* 30 g./l. in benzene and *ca.* 25 g./l. in *iso*propyl alcohol.

Preparation of Thorium Tetramethoxide.—Thorium tetra*iso*propoxide (5·8 g.) was dissolved in benzene (50 g.). Methyl alcohol (130 g.) was added, a white gelatinous solid being precipitated. The mixture was boiled for 1 hr. and then evaporated to dryness. Analysis of the solid product (4·6 g.) (Found: Th, 65·0; OMe, 29·4%) suggested that interchange was not complete. The product was treated with more methyl alcohol (150 g.), and a white powder remained after evaporation to dryness [Found: Th, 66·6; OMe, 31·6. Calc. for $Th(OMe)_4$: Th, 65·2; OMe, 34·8%]. A sample of the methoxide was heated at 320°/0·05 mm. for 2 hr.; no sublimation occurred although the residue had decomposed (Found: Th, 71·4; OMe, 25·7%).

One of us (M. A. S.) thanks Alexandria University for study-leave.

BIRKBECK COLLEGE, MALET STREET, W.C.1. [*Received, December 9th*, 1953.]

A Kinetic Study of the Formation and Hydrolysis of tert.-*Butyl Hypochlorite.*

By M. ANBAR and I. DOSTROVSKY.

[Reprint Order No. 4655.]

The formation of *tert.*-butyl hypochlorite from the alcohol and hypochlorous acid and its hydrolysis have been investigated in a series of buffer solutions ranging in pH from 6·3 to 2·7. By the use of ^{18}O as tracer it has been shown that in both reactions the bond between the *tert.*-butyl group and the oxygen atom remains intact. Kinetic investigations showed the reaction to be subject to general acid–base catalysis. The rate coefficients for a number of catalysts have been determined. A mechanism of these reactions is postulated involving various active intermediates such as H_2OCl^+, acetyl hypochlorite, and other related compounds of the type ACl, where A is the anion of any general acid. The relationship between the reactions of *tert.*-butyl hypochlorite and those of hypochlorous acid is discussed.

As part of a broader investigation we have examined the formation and hydrolysis of *tert.*-butyl hypochlorite. This ester was chosen because it is one of the most stable of alkyl hypochlorites and because of the interest in its reactions with various organic compounds.

Alkyl hypochlorites are formed readily when chlorine is passed into a solution of an alcohol in aqueous alkali, and also when an alcohol is treated with sodium hypochlorite solution (Sandmeyer, *Ber.*, 1885, **18**, 1767; 1886, **19**, 859; Chattaway and Backeberg, *J.*, 1923, **123**, 2999). *tert.*-Butyl hypochlorite is also formed easily by the action of the alcohol on free hypochlorous acid in aqueous solution or on chlorine monoxide in carbon tetrachloride solution. On the other hand, it undergoes rapid hydrolysis when shaken with dilute alkali, but remains unchanged after prolonged shaking with aqueous acid. These apparently conflicting results are now to be explained.

As a first stage in the elucidation of the mechanisms of the hydrolysis and formation reactions of *tert.*-butyl hypochlorite, we have determined the mode of fission of the hypo-

chlorite linkage. The alternative modes of bond breaking are shown in the reaction schemes below, where the dotted line represents the linkage which is broken :

$$Bu^tO\cdots Cl + H_2O \rightleftharpoons H{-}O\cdots Cl + Bu^tO\cdots H \quad (1)$$

$$Bu^t\cdots O{-}Cl + H_2O \rightleftharpoons H\cdots O{-}Cl + Bu^t\cdots O{-}H \quad (2)$$

By the use of compounds labelled with ^{18}O it is possible to distinguish between the two paths. Formation reactions were carried out by starting with alcohol of normal isotopic composition and water enriched in ^{18}O and also with alcohol enriched in ^{18}O and normal water. The results of the isotopic experiments are summarised in Table 1.

TABLE 1. *Isotopic changes in the formation of* tert.*-butyl hypochlorite.*

	Atom % excess of ^{18}O in aqueous medium	Atom % excess of ^{18}O in *tert.*-butanol	Atom % excess of ^{18}O in *tert.*-butyl hypochlorite	Atom % excess of ^{18}O in water recovered
N-NaOH...	0·85	0·00	0·00	0·84
	0·00	0·86	0·79	0·00
N-$HClO_4$...	0·00	0·86	0·76	0·00

A similar study was made of the hydrolysis of *tert.*-butyl hypochlorite, starting with ^{18}O-labelled compound and normal water, and also in one case starting with enriched water and normal hypochlorite. The results are presented in Table 2.

TABLE 2. *Isotopic changes in the hydrolysis of* tert.*-butyl hypochlorite.*

	Atom % excess of ^{18}O in aqueous medium	Atom % excess of ^{18}O in *tert.*-butyl hypochlorite	Atom % excess of ^{18}O in *tert.*-butanol
5N-NaOH	0·00	0·86	0·85
	0·00	0·79	0·78
	0·87	0·00	0·00
1N-$HClO_4$	0·00	0·79	0·77

The isotopic data show unambiguously that the formation and hydrolysis reactions proceed under all conditions according to scheme (1), the bond between the alkyl group and the oxygen atom remaining intact throughout. Isotopic results alone, however, are not sufficient to indicate details of mechanism although they limit considerably the number of possible reaction schemes. Further information regarding these reactions was sought by a kinetic investigation.

No chemical method is available for following the rate of interconversion of hypochlorous acid and an alkyl hypochlorite, since the two materials undergo identical reactions with most reagents. However, it was shown by the authors (*J.*, 1954, 1105) that differences exist in the ultra-violet absorption spectra of the two compounds. Use was made of these differences for following the progress of hydrolysis or formation reactions, the change of ultra-violet light absorption with time representing the rate of reaction. Rate constants were calculated from the formula

$$k_{obs.} = (1/2{\cdot}3t) \log (D_\infty - D_0)/(D_\infty - D_t) \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where $k_{obs.}$ is the rate constant of the reaction, and D_0, D_t, and D_∞ are the optical densities at times 0, t, and ∞. Since these reactions are reversible, and of first order either way, the observed rate constant $k_{obs.}$ is composed of the sum of the rate constants of the forward and the reverse reaction, $k_{obs.} = k_f + k_h$. Whenever possible the rate constants were observed both for the formation and for the hydrolysis reaction and the means of these results used. The observed rate constant may be resolved into its components with the aid of the equilibrium constant for the reaction. It can be readily shown that

$$K\frac{[H_2O]}{[Bu^tOH]} = \frac{C(\varepsilon_2 - \varepsilon_1)}{C\varepsilon_2 - D_\infty} - 1 \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where K is the equilibrium constant for the hydrolysis reaction, C the initial concentration of *tert.*-butyl hypochlorite, and ε_1 and ε_2 the extinction coefficient of *tert.*-butyl hypochlorite and hypochlorous acid in l. mole^{-1} cm.$^{-1}$. From over 200 experiments the value of K at

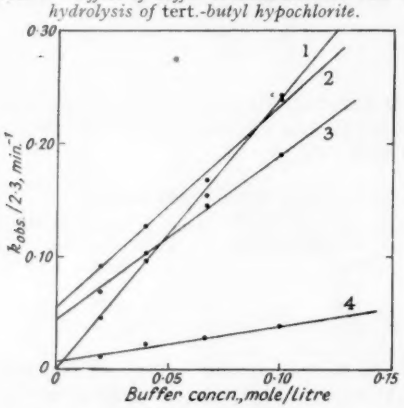
25° has been obtained as 0·024 ± 0·003. Most of the rate constants presented in this paper have not been resolved into their components.

The reactions were carried out in aqueous solutions containing some *tert.*-butanol (usually 1·55 mole/l.) and maintained at the appropriate pH value by means of buffers. The presence of *tert.*-butanol is necessary in order to ensure complete solubility of the *tert.*-butyl hypochlorite. The rates were found to depend both upon the pH of the solution and upon the buffer concentration. For runs at constant pH and ionic strength the rates were found to be a linear function of the buffer concentration :

$$k_{obs.} = k' + k_{buffer} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

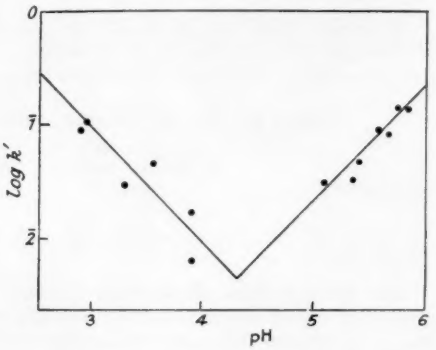
For each value of pH a set of such linear equations was obtained, and after solving them by the method of least squares, the constants k' and k_{buffer} were obtained. A few of the

FIG. 1. *Effect of buffer concentration on rate of hydrolysis of* tert.*-butyl hypochlorite.*



1, Acetate buffer, pH 4·5.
2, Phosphate buffer, pH 5·85.
3, Acetate buffer, pH 5·4.
4, Phosphate buffer, pH 3·9.

FIG. 2. *Effect of* pH *on rate of hydrolysis and formation of* tert.*-butyl hypochlorite.*



results are tabulated in Table 3, and as an illustration plots of $k_{obs.}$ against buffer concentration for various pH values are shown in Fig. 1.

TABLE 3. *Values of k' and k_{buffer} for the hydrolysis and formation of* tert.*-butyl hypochlorite at various* pH *values at 25°.*

pH	k', min.$^{-1}$ × 10^2	k_{buffer}, l./mole/min. acetate	phosphate	pH	k', min.$^{-1}$ × 10^2	k_{buffer}, l./mole/min. acetate	phosphate
2·90	9·0	8·2	—	5·43	4·2	2·2	—
2·95	10·3	—	3·3	5·58	8·6	—	3·18
3·57	7·2	4·65	—	5·75	13	1·8	—
3·9	1·7	—	0·72	5·85	13	—	4·0

The constants k' and k_{buffer} obtained in this way are composite and require further resolution. In Fig. 2 the values of log k' are plotted against pH and, as will be noticed, a pronounced minimum in the rate occurs at a pH value of about 4·4. For the purpose of this paper we shall refer to media with pH values lower than 4·4 as acid, and those with pH higher than 4·5 will be called basic. It is apparent that the reaction is catalysed both by hydrogen and by hydroxyl ions and therefore k' should be of the form

$$k' = k_w + k_H[H^+] + k_{OH}[OH^+] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

where k_w is the rate coefficient of the uncatalysed reaction, and k_H and k_{OH} are the catalytic rate coefficients for the hydrogen and the hydroxyl ion, respectively. Again applying the

method of least squares to the set of these equations, we obtain the following values for the three constants: $k_w = 1{\cdot}6 \times 10^{-4}$ min.$^{-1}$; $k_H = 1{\cdot}3 \times 10^{2}$ l. mole^{-1} min.$^{-1}$; $k_{OH} = 2{\cdot}7 \times 10^{7}$ l. mole^{-1} min.$^{-1}$ at 25°. Equation (4) can be rewritten in the form:

$$k' = k_w + k_H[H^+] + k_{OH} \times 10^{-14}/[H^+] \quad . \quad . \quad . \quad . \quad . \quad (4a)$$

and from this the pH value for which a minimum in the rate should occur can be calculated to be

$$[H^+] = 10^{-7}\sqrt{k_{OH}/k_H}$$

Substituting the values obtained above in this equation, we obtain for $pH_{min.}$ the value 4·4, and for the minimum rate the value $\sim 10^{-2}$ min.$^{-1}$.

The total buffer catalytic coefficient, k_{buffer}, can be written as

$$k_{buffer} = k_{HA}[HA] + k_{A^-}[A^-] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

where k_{KA} and k_{A^-} are the catalytic rate coefficients for the buffer acid and its anion respectively. Using a technique identical with that used for obtaining the other catalytic coefficients, we obtained the values for k_{HA} and k_{A^-}. The general expression for the observed rate constant is therefore given by:

$$k_{obs.} = k_w + k_H[H^+] + k_{[OH]}[OH^-] + \Sigma k_{HA}[HA] + \Sigma k_{A^-}[A^-] \quad . \quad . \quad (6)$$

which is the classical expression for a case of general acid–base catalysis. In Table 4 are presented the catalytic rate coefficients for a number of acid anions derived from an analysis of the observed rates by the methods outlined above. It should be noted that each of the constants presented in Table 4 is derived from some 300 separate kinetic runs.

TABLE 4. *Catalytic constants of acids and their conjugate bases for the formation and hydrolysis reactions of* tert.-*butyl hypochlorite at* 25·2° *and aqueous* 1·55M-tert.-*butanol solution.*

Acid	k_{HA}	k_{A^-}	Acid	k_{HA}	k_{A^-}	Acid	k_{HA}	k_{A^-}
H_3O^+ ...	$1{\cdot}1 \times 10^{2}$	$<10^{-4}$	$CH_3{\cdot}CO_2H$	5·7	$3{\cdot}1 \times 10^{-1}$	HClO ...	$2{\cdot}4 \times 10$	$9{\cdot}1 \times 10^{3}$
H_3PO_4 ...	$8{\cdot}2 \times 10$	$1{\cdot}1 \times 10^{-2}$	$H_2PO_4^-$ ...	3·6	$4{\cdot}5 \times 10$	H_2O	$<10^{-4}$	$2{\cdot}3 \times 10^{7}$

Hypochlorous acid and the hypochlorite ion are both catalysts for the hydrolysis and the formation reaction. This fact causes a certain amount of trouble in interpreting the kinetic measurements, for the concentration of these materials changes in the course of the reaction. This effect can be seen from the results of Table 5, where the observed rates are tabulated for various initial concentrations of hypochlorous acid.

TABLE 5. *The effect of initial concentration of hypochlorous acid on the rate of formation of* tert.-*butyl hypochlorite in* M/50-*acetate buffer solution and at* pH 4·7.

$10^3 \times$ Initial concn. (M) of HOCl	17·7	15·3	12·0	9·45	6·45
$10^3\ k_{obs.}$, min.$^{-1}$	262	249	235	226	205

Fortunately, the catalytic coefficients of hypochlorous acid and its ion are sufficiently small to be neglected, except in the region of the rate minimum and low buffer concentrations. From experiments in this range the value of the catalytic coefficients for hypochlorous acid (and ion) and other weak acids can be determined. The resolution of the kinetic data to yield various coefficients in this range is complicated by the presence of the square term in the rate equations. We may write for experiments with constant buffer composition and concentration:

$$d[HOCl]/dt = -[HOCl]\{k_1[HOCl] + k'\} + [BuOCl]\{k_2[HOCl] + k''\} \quad . \quad . \quad (7)$$

where k_1 and k_2 are the catalytic coefficients of HOCl for the formation and the reverse reaction, and k' and k'' are of the form $\Sigma k_i C_i$, where k_i is the catalytic coefficient of the catalyst i present in the concentration C_i.

Setting $[Bu^tOCl] + [HOCl] = C$, and $[HOCl] = x$, we have

$$dx/dt = -(k_1 + k_2)x^2 - [(k' + k'') - k_2C]x + k''C$$

This equation may be rewritten in the form

$$dx/dt = px^2 + qx + r = p(x - x_\infty)(x - x'_\infty)$$

where $p = -(k_1 + k_2)$, $q = -[(k' + k'') - k_2C]$, $r = k''C$, and x_∞ and x'_∞ are the roots of the quadratic equation $px^2 + qx + t = 0$. The differential equation may be integrated to give

$$1 + \Delta/(x - x_\infty) = Re^{-p\delta t}$$

where $\Delta = x_\infty - x'_\infty$ and R is the integrating factor. Observing x at constant intervals of time, *e.g.*, at t_i, $t_i + \delta$, $t_i + 2\delta$, we may write $(1 + \Delta y_{i+1})/(1 + \Delta y_i) = e^{-p\delta t}$, which can be rearranged to $1 + \Delta y_{i+1} = E(y_{i+1} - y_i)$, where $y_i = 1/(x_i - x_\infty)$ and $E = \Delta/(e^{-p\delta t} - 1)$. Solution of the last equation by the method of least squares gives values of Δ and E, and thence the values of $p = -(k_1 + k_2)$; k'' can then be easily obtained if it is remembered that $k''C = r - px_\infty x'_\infty$ and that $x'_\infty = x_\infty - \Delta$.

The order of this reaction with respect to *tert.*-butanol is of some interest. In the runs described so far this reagent was present in great and constant excess, and no information as to the order of the reaction with respect to it could be derived. A number of reactions were carried out using varying concentrations of *tert.*-butanol; the results are tabulated in Table 6. From Expts. 58, 59, 60 and 216, 217, it is clear that the rate of reaction is independent of alcohol concentration. Interpretation of the results at higher concentrations of alcohol is complicated by the operation of a complex solvent effect. Variation of the proportion of alcohol or dioxan in the medium affects simultaneously several of the reaction parameters. In addition to the direct effect of the change of medium on the rate-controlling process, the dissociation constant of the buffer acid and the activity of hydrogen or hydroxyl ions will also be affected. The direction and magnitude of the

TABLE 6. *Rates of formation and hydrolysis of* tert.*-butyl hypochlorite in presence of varying concentrations of* tert.*-butanol and dioxan.*

Expt. No.	Buffer acid concn.	Ratio of buffer acid to buffer anion	Molarity of *tert.*-butanol	Vol. % of dioxan	$10^3\ k_{obs.}$, $min.^{-1}$
34	M/50-Phosphate	196 : 4	3·6	0	60
35	($H_2PO_4^-$; $HPO_4^=$)	,,	2·7	0	54
30	,,	,,	1·55	0	38
36	,,	,,	0·68	0	35
39	,,	,,	0·35	0	29
58	,,	3 : 1	0·68	0	200
59	,,	,,	0·35	0	190
60	,,	,,	0·18	0	180
214	M/25-Acetate	1 : 1	1	0	420
215	,,	,,	1	9·0	1000
216	,,	,,	1	28·6	1140
217	,,	,,	0·125	28·6	1160
225	M/50-Acetate	4 : 1	1·55	0	260
226	,,	,,	0·48	0	440
227	,,	,,	0·125	0	830

latter effects are known (cf. Conway, "Electrochemical Data," Elsevier, Amsterdam, 1952, p. 196). The presence of increasing quantities of dioxan or *tert.*-butanol will cause a decrease in the concentration and activity of the hydrogen ion as compared with identical buffer solution in pure water. The effect of this on the reactions under study will be analogous to an apparent shift of pH to a higher value, and will be different on either side of the minimum in the rate. On the acid side, the addition of alcohol or dioxan will cause a reduction in the rate (cf. Expts. 225—227), whilst on the alkaline side a similar addition will cause an increase in the rate (cf. Expts. 58, 59). This effect is superimposed on that of solvent variation on the reaction rate, and the result will depend on the relative magnitude and direction of the two effects. It is therefore impossible to derive unambiguous results from the effect of solvent on the rate-determining process, and to use this safely in considerations of the mechanisms of these reactions. Somewhat similar considerations

apply to the effect of changing ionic strength of the media on the reaction rates (see Table 7).

TABLE 7. *Effect of ionic strength of the buffer solution on the rate of formation and hydrolysis of* tert.-*butyl hypochlorite.*

Buffer solution, M/50		$k_{obs.}$, min.$^{-1}$ × 10^3 At μ = 0·05	At μ = 0·45	Buffer solution, M/50		$k_{obs.}$, min.$^{-1}$ × 10^3 At μ = 0·05	At μ = 0·45
Phosphate buffer	pH 5·5	250	1850	Acetate buffer	pH 5·7	420	560
	,, 5·3	330	1700		,, 5·4	1060	1210
	,, 4·8	160	1240		,, 3·8	440	530
	,, 4·6	160	900		,, 3·6	580	650
	,, 3·3	330	1090				

DISCUSSION

The kinetic and isotopic data presented in the preceding pages may be interpreted by the following general mechanism;

$$\left.\begin{array}{l} HOCl + HA \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ACl + H_2O \\ ACl + BuOH \rightleftharpoons BuOCl + HA \end{array}\right\} \text{acid region}$$

$$\left.\begin{array}{l} HOCl + A^- \underset{k_{-2}}{\overset{k_1}{\rightleftharpoons}} ACl + OH^- \\ ACl + BuO^- \rightleftharpoons BuOCl + A^- \end{array}\right\} \text{alkaline region}$$

This mechanism leads to first-order kinetics, the rate constants being given, assuming that [ACl] remains very small throughout, by expressions of the type

$$k' = k_{HA}[HA](k_1k_2[H_2O] + k_1k_2[ROH])/(k_1([H_2O] + k_2[ROH])$$

An essential feature of this mechanism is the participation of the intermediate ACl, derived from the catalyst HA, by a process which may be regarded either as a nucleophilic substitution on the halogen of hypochlorous acid or alkyl hypochlorite, or as a chlorination of the active hydrogen of the catalysts. For a substance HA to be an effective catalyst for the formation and hydrolysis reactions of alkyl hypochlorites, it must react with hypochlorous acid or the alkyl hypochlorite to form an intermediate compound, more reactive with respect to chlorination and hydrolysis than the parent compounds. The catalyst need not necessarily be an acid, although most of the common examples belong to this class, and in the general case the rate-determining step is not the transfer of a proton to HOCl or Bu^tOCl.

The effectiveness of the intermediate ACl as a chlorination agent can be correlated with the electronegative character of the group A, since the more positive the chlorine atom is in these compounds, the readier will be its attack on a nucleophilic centre. Increasing the electronegativity of the group A will make the intermediate more reactive, and as a consequence a parallelism should exist between the activity of the intermediate and the strength of the acid from which it is derived. Using these considerations, we may arrange the following compounds in the order of their activity as halogenating agents:

$Bu^tOCl < (Bu^tOHCl)^+$; $Bu^tOCl < HOCl < CH_3{\cdot}COCl$; $HOCl < (H_2OCl)^+$; $HOCl < Cl_2O < Cl_2$

Some of the catalysts encountered in our work, and the active intermediates derived from them, are listed in Table 8.

TABLE 8. *Catalysts and active intermediates in the formation and hydrolysis of alkyl hypochlorites.*

Catalysts ...	H_2O	H_3O^+	$CH_3{\cdot}CO_2H$	H_3PO_4	$H_2PO_4^-$	HPO_4^{2-}	HOCl	HCl	H_2SO_4	ROH
Intermediates	HOCl	H_2OCl^+	$CH_3{\cdot}CO{\cdot}OCl$	H_2PO_4Cl	HPO_4Cl^-	PO_4Cl^{2-}	Cl_2O	Cl_2	HSO_4Cl	ROCl

A more detailed consideration of these catalysts will be presented below.

A special case of the general mechanism presented above occurs when the catalyst is the hydroxonium ion, H_3O^+:

$$HOCl + H_3O^+ \underset{}{\overset{k_1}{\rightleftharpoons}} H_2OCl^+ + H_2O$$
$$H_2OCl^+ + BuOH \rightleftharpoons HOCl + BuOHCl^+$$
$$BuOHCl^+ + H_2O \underset{k_{-3}}{\rightleftharpoons} BuOCl + H_3O^+$$

with k_1 and k_{-3} rate the controlling. The intermediates in this case are the conjugate acids of hypochlorous acid and the alkyl hypochlorite. The mechanism has been expressed as proceeding in three stages in order to maintain the symmetry between the formation and the hydrolysis reactions; since, if in the formation reaction an intermediate of the type H_2OCl^+ is assumed, there seems to be no reason for excluding the intermediate $BuOHCl^+$ in the hydrolysis reaction. The rate-determining step in this special case is actually the proton transfer to the HOCl and BuOCl molecules.

For the acid region only, it is possible to formulate a general reaction scheme involving only proton transfers as rate-determining steps:

$$HOCl + HA \rightleftharpoons H_2OCl^+ + A^-$$

However, according to this formulation only one active intermediate is possible, H_2OCl^+, a limitation which appears to be unnecessarily severe, particularly as in the reactions in the alkaline region, where no generalisation based on rate-determining proton transfers is possible, we assume the existence of intermediates ACl, and we have already seen that such compounds are at least as reactive as is H_2OCl^+. We therefore prefer the more general formulation presented above.

Combining the expression for the catalytic rate coefficients (p. 1099) of the hydrolysis and formation reactions with that of the equilibrium constant, and substituting its value ($K = k_{-1}k_{-2}/k_1k_2 = 0{\cdot}024$, cf. p. 1095), we can show that, provided k_1 is not much smaller than k_{-2} and excepting solvent effects, the observed rate constant will not be particularly sensitive to changes in alcohol concentration. On general considerations (p. 1099) we should expect k_1 to be always somewhat greater than k_{-2}, and our observation of the relative independence of the rate on alcohol concentration is in complete accord with the mechanism postulated above (cf. Table VI). It follows from the same considerations that the observed rate constants will have a value between k_1 and k_{-2}, and since these rate coefficients probably do not differ very greatly from one another, we may take the observed rate constant as representing approximately the rate of formation of the active intermediate ACl. The observed catalytic coefficients discussed below have been interpreted in this way.

Another special case of our general mechanism arises in the alkaline region, if unbuffered solutions are used and the sole reagent is the hydroxyl ion. The reaction scheme then reduces to:

$$HOCl + BuO^- \rightleftharpoons BuOCl + OH^-$$

In these circumstances the rate of reaction should be of first order with respect to alcohol. However, we have not succeeded in measuring rates of reaction in unbuffered alkaline solution, and even in the most favourable case, the contribution of the buffer ions to the total rate outweighed that of the hydroxyl ion, and made the rate independent of alcohol concentration.

It is important to note, that even under the alkaline conditions used in this work, the reaction is between un-ionised hypochlorous acid and the catalyst or butoxide ion. The catalytic effect of the hydroxide ion on the formation reaction is accordingly due to its effect on the concentration of the butoxide ion. The rate equation for the formation reaction can be written as

$$v_f = k[HOCl][BuO^-] + k'[HOCl][A^-]$$

and since $[BuO^-] = K[BuOH][OH^-]$, the equation may be rewritten in the form

$$v_f = [HOCl](k''[BuOH][OH^-] + k'[A^-])$$

Soper and Smith (*J.*, 1926, 1582) have also demonstrated that the chlorination of phenol occurs by reaction between un-ionised hypochlorous acid and the phenoxide ion and not between phenol and hypochlorite ion. A great increase in the hydroxyl-ion concentration to the point where ionisation of hypochlorous acid becomes appreciable would be expected to cause a decrease in the rate commensurable with the decreased concentration of free acid. We have not succeeded in obtaining rate constants at such high pH values, but the effect may be illustrated adequately by examples taken from the preparative chemistry of alkyl hypochlorites. No *tert.*-butyl hypochlorite is formed when *tert.*-butanol is added to a strongly alkaline solution of sodium hypochlorite. It is only when the pH of the solution is reduced to below 10 that rapid separation of the hypochlorite takes place. Similarly, when chlorine is passed through an alkaline solution of *tert.*-butanol, no hypochlorite is formed until most of the alkali has been destroyed by the chlorine, whereupon a sudden separation of *tert.*-butyl hypochlorite occurs. These facts are interpreted as due to the small concentration of free hypochlorous acid in strongly alkaline solution, and the consequent suppression of the formation reaction. As the pH of the solution is reduced below 10, the concentration of un-ionised hypochlorous acid increases rapidly, and reaction with *tert.*-butoxide ions ensues.

We turn now to a more detailed discussion of the various reaction intermediates. The ion H_2OCl^+ has been assumed by Derbyshire and Waters (*J.*, 1951, 73) to be the intermediate in the acid-catalysed chlorination of sodium toluene-*p*-sulphonate by hypochlorous acid, this being analogous to the intermediate $(H_2OBr)^+$ suggested for the acid bromination of the same compound (Derbyshire and Waters, *J.*, 1950, 564; Derbyshire, *Research*, 1952, **5**, 240). Derbyshire and Waters (*loc. cit.*) used rather high concentrations of acid (0·3—4M) to obtain reasonable rates of chlorination, and the kinetics were of first order in the toluenesulphonate. Using the more reactive materials, phenol and anisole, and lower concentrations (0·01—0·1M) of strong acids as catalysts, de la Mare, Hughes, and Vernon (*Research*, 1950, **3**, 192, 242) obtained rates of chlorination which were of zero order with respect to the compound substituted, and concluded that the observed rate was that of production of the positive chloronium ion Cl^+ from HOCl and a strong acid. This conclusion was criticised by Shilov (*Doklady Akad. Nauk U.S.S.R.*, 1952, **84**, 1001), who interpreted these results in terms of rate-controlling production of free chlorine from HOCl and traces of chloride ion. However, it appears from the note of de la Mare, Hughes, and Vernon (*loc. cit.*) that this possibility is excluded by the experimental precautions. In any case, the rate-controlling reaction in the chlorinations described by them cannot be the same as that found in our work. For the rate constant reported by these authors, $3{\cdot}1 \times 10^{-4}$ sec.$^{-1}$, is some 10^4 times slower than the rate-controlling step found by us under similar conditions (cf. Table 4). We interpret this difference as due to the fact that, whereas the rate observed in our case is that of the formation of H_2OCl^+, *i.e.*, the rate of proton transfer to HOCl, the rate observed by de la Mare, Hughes, and Vernon (*loc. cit.*) is that of subsequent decomposition of the H_2OCl^+ ion into Cl^+ and water. H_2OCl^+ is a less effective chlorinating agent than Cl^+ and cannot effect the chlorination of an aromatic compound, yet it is sufficiently active to effect the conversion of alcohols into hypohalites. We may illustrate our point by considering the sequence of events which will take place upon the chlorination by acidified hypochlorous acid of a series of compounds of increasing reactivity. With the least reactive compound a first-order rate with respect to substrate will be observed, changing to a zero-order rate with more reactive compounds, the rate then representing the rate of formation of Cl^+. With still more reactive compounds a first-order rate will again be observed corresponding to the reaction between H_2OCl^+ and the substance examined. With the most reactive compounds a second zero-order reaction with respect to substrate will be observed, the rate then representing the rate of formation of H_2OCl^+.

It should be noted that the rate of proton transfer to hypochlorous acid observed in the present work is probably the first measurement of such a transfer to a simple inorganic molecule (cf. Bell, " Advances in Catalysis," Vol. IV, Acad. Press, 1952, p. 135).

The chlorination of phenols may also be explained in these terms. The phenolic hydrogen is probably chlorinated rapidly to give the hypochlorite which is in equilibrium

with hypochlorous acid and $(H_2OCl)^+$, the chlorination of the aromatic ring occurring by Cl^+, which is produced by the decomposition of the protonated hypochlorous acid (cf. Arkhangelskaya and Likhosherstov, *J. Gen. Chem. U.S.S.R.*, 1937, **7**, 1914).

In Table 8, Cl_2 appears as a possible intermediate if chloride ions are present. In such circumstances there will be an additional term in the general catalytic equation (6) (p. 1097). According to our method of analysis, and the concentration of Cl^- being assumed to be constant and due to traces of chloride in the reagents and solvent, this term will be included in the spontaneous " water reaction," k_w. We have already demonstrated that this term is negligibly small, and thus the contribution of Cl_2 in our reactions is not significant. It may well be that the accuracy of our results is somewhat reduced by chance variation in the amounts of traces of chloride present.

Acetyl hypochlorite or chlorine acetate, $CH_3{\cdot}CO{\cdot}OCl$, has been shown to be easily formed under conditions similar to those prevailing in this study (Anbar and Dostrovsky, *J.*, 1954, 1105), and the assumption that this substance is an active intermediate is quite reasonable. A similar assumption has been made by de la Mare, Ketley, and Vernon (*Research*, 1953, **6**, 125) in their study of chlorinations in media containing acetic acid. For very active substances a zero-order rate with respect to the substrate has been observed by them, and the observed rate taken to be the rate of formation of acetyl hypochlorite. In view of the difference in the media used, their rate (0·05 l. mole^{-1} min.$^{-1}$) is in good agreement with our catalytic coefficient for acetic acid (cf. Table 4) which represents the rate of formation of acetyl hypochlorite. Acetyl hypochlorite has also been shown to be an active intermediate in the chlorohydrin formation reaction of allyl alcohol (Israel, *J.*, 1950, 1286), and the catalytic constant for its formation from acetic acid (14·5 l. mole^{-1} min.$^{-1}$) is in better agreement with our value (5·7 l. mole.$^{-1}$ min.$^{-1}$). Mauger and Soper (*J.*, 1946, 41) and Painter and Soper (*J.*, 1947, 342) have shown that acyl hypohalites are active intermediates in *N*-chlorination reactions and in the iodination of phenol.

The action of hypochlorous acid as a catalyst had already been mentioned in connection with the complication it introduces into the kinetics. The active intermediate derived from hypochlorous acid is chlorine monoxide. Its rate of formation from hypochlorous acid and from *tert.*-butyl hypochlorite is governed by the catalytic coefficient of HOCl. The value for this coefficient (Table 4) is somewhat higher than that reported by Israel, Martin, and Soper (*J.*, 1950, 1282), *viz.*, 8·2 l. mole^{-1} min.$^{-1}$, and much higher than Shilov's value (*loc. cit.*), *viz.*, 1·6 l. mole^{-1} min.$^{-1}$. Chlorine monoxide is also an active intermediate in the addition reactions of hypochlorous acid to unsaturated linkages (cf. Shilov, *loc. cit.*; Israel, *J.*, 1950, 1286).

Some of the other catalysts of Table 8 have been assumed also by others. Thus Derbyshire and Waters (*J.*, 1951, 73) mention the probable participation of chlorine sulphate in chlorination reaction, and chlorine phosphate is probably an intermediate in the addition reactions studied by Shilov (*Doklady Akad. Nauk U.S.S.R.*, 1951, **81**, 435, 1621).

Experimental

(A) *Experiments with Compounds labelled with* ^{18}O.—*Preparation of materials.* *tert.*-Butyl alcohol labelled with ^{18}O was prepared by two methods.

(*a*) Acetone (58 g.) was dissolved in water enriched in ^{18}O (180 c.c. of 0·82 atom % excess of ^{18}O), concentrated sulphuric acid (2 ml.) was added, and the mixture refluxed for 1 hr. After neutralisation with metallic calcium, the mixture was filtered, and the acetone recovered quantitatively by fractional distillation. Labelled acetone (0·5 mol., 29 g.) thus obtained was added to a solution of Grignard reagent prepared from magnesium (12 g.) and excess of methyl bromide. When the addition of acetone had been completed, the mixture was decomposed by addition of water (250 ml.). After separation of the solids, the aqueous layer was fractionally distilled, and the *tert.*-butanol fraction dried (K_2CO_3). The alcohol obtained contained 0·78 atom % excess of ^{18}O. The yield of alcohol was only 30% based on acetone taken. The following method of preparation proved to be more convenient and efficient and was used in all subsequent preparations.

(*b*) *tert.*-Butyl acetate (116 g., 1 mole) (*Org. Synth.*, 1944, **24**, 18) was added to water enriched

in ^{18}O (180 g.; 0·88 atom % excess of ^{18}O). After addition of concentrated sulphuric acid enriched in ^{18}O (10 ml.; 0·81 atom % excess of ^{18}O) the mixture was refluxed until a clear solution was obtained (about 1 hr.). On cooling, metallic calcium equivalent to the sulphuric acid was added, and the solution was filtered and fractionated. The alcohol was dried by azeotropic distillation with benzene; the yield was 70% based on ester. The alcohol contained 0·86 atom % excess of ^{18}O. From the residual solution acetic acid enriched with ^{18}O was isolated by distillation.

The enriched sulphuric acid used in this preparation was made in the following manner. To analytical-grade sulphur (32 g.) in a 3-necked flask, fitted with reflux condenser and dropping funnel, was added water enriched in ^{18}O (80 ml.; 0·81 atom % excess of ^{18}O), and the mixture stirred. Through a dropping funnel, bromine (300 g.) was added as fast as its colour disappeared. Towards the end of the reaction it was necessary to heat the mixture. When all the sulphur had dissolved, the mixture was distilled until the temperature of the residue reached 130°. After addition of a few drops of nitric acid to oxidise impurities, the pressure was reduced and the distillation continued until the temperature reached 220° (at 100 mm. Hg). The residue consisted of pure sulphuric acid of 99% concentration.

Reactions with Labelled Compounds.—(a) *Formation of* tert.-*butyl hypochlorite in alkaline medium.* *tert.*-Butyl hypochlorite was prepared by passing chlorine through a solution of labelled *tert.*-butanol (20 g.; 0·86 atom % excess of ^{18}O) in 10% sodium hydroxide solution (200 ml.) of normal isotopic composition. When a layer of *tert.*-butyl hypochlorite had formed, the flow of chlorine was stopped, and the hypochlorite layer separated, washed with 10% sodium hydrogen carbonate solution, and dried (K_2CO_3). The *tert.*-butyl hypochlorite so obtained was analysed for the isotopic proportion of the oxygen atoms as follows. *tert.*-Butyl hypochlorite (1 ml.) was added to toluene (1 ml.) in a small flask fitted with a small reflux condenser. The flask was exposed to sunlight until the yellow colour of the hypochlorite was destroyed (3—5 min.), and the *tert.*-butanol which formed was separated by fractionation from the benzyl chloride and excess of toluene. The alcohol was analysed for its isotopic composition by the method of Anbar, Dostrovsky, Klein, and Samuel (to be published), and found to contain 0·79 atom % excess of ^{18}O.

This reaction was repeated with *tert.*-butanol of normal isotopic content and water enriched with ^{18}O (200 ml. of 10% sodium hydroxide solution, 0·85 atom % excess of ^{18}O). The hypochlorite was isolated and analysed as described above. The alcohol obtained finally had normal isotopic composition.

(b) *Formation of* tert.-*butyl hypochlorite in acid medium.* ^{18}O-Labelled *tert.*-butanol (4 g., 0·86 atom % of ^{18}O) was dissolved in 200 ml. of an aqueous solution 0·4N with respect to hypochlorous acid and 1N to perchloric acid, all of normal isotopic composition. Carbon tetrachloride (15 ml.) was added, and the mixture shaken for 15 min. at room temperature. The carbon tetrachloride layer was separated, dried (K_2CO_3), and shaken with N-sodium hydroxide solution (100 ml.) of normal isotopic composition until the yellow colour disappeared. The carbon tetrachloride layer was separated, and the aqueous layer fractionated to obtain *tert.*-butanol. The alcohol was dried and analysed for its isotopic composition, and found to contain 0·76 atom % excess of ^{18}O.

(c) *Hydrolysis of* tert.-*butyl hypochlorite in alkaline media.* *tert.*-Butyl hypochlorite of normal isotopic composition (2 ml.) was added to 5N-sodium hydroxide (7 ml.; 0·87 atom % excess of ^{18}O) and shaken in a separating funnel for a few minutes. The alcohol was isolated by salting out, dried twice (K_2CO_3), and analysed, and found to have a normal isotopic composition. The labelled sodium hydroxide used in this experiment was prepared by decomposing 3% sodium amalgam with the appropriate amount of enriched water. The hydrolysis experiment was repeated with use of normal water and labelled *tert.*-butyl hypochlorite [obtained as under (*a*) above]. Starting with hypochlorite of isotopic composition 0·86 atom % of ^{18}O, an alcohol was obtained containing 0·85 atom % of ^{18}O. In a duplicate experiment a hypochlorite of 0·79 atom % of ^{18}O yielded an alcohol containing 0·78 atom % of ^{18}O.

(d) *Hydrolysis of* tert.-*butyl hypochlorite in acid media.* ^{18}O-Labelled *tert.*-butyl hypochlorite (2 ml., 0·79 atom % excess) was dissolved in N-perchloric acid of normal isotopic composition (200 ml. were necessary for homogeneous solution). After ½ hr., the mixture was made alkaline with sodium hydroxide pellets and distilled. The first 10 ml. of the distillate were collected and fractionated. The *tert.*-butanol azeotrope was dried twice (K_2CO_3) and analysed; it contained 0·77 atom % excess of ^{18}O.

Kinetic Measurements.—*Materials.* *tert.*-Butyl hypochlorite was prepared by Chattaway and Backeberg's method (*J.*, 1923, **123**, 2999), and hypochlorous acid by that of Shilov and

Gladtchikova (*J. Amer. Chem. Soc.*, 1938, **60**, 490). *tert.*-Butyl alcohol was purified by careful fractionation through a 40-plate column. Reaction media for the hydrolysis reaction were prepared by diluting the required proportions of stock solutions of the buffer components to the appropriate total concentration with distilled water and adding the calculated amount of pure sodium perchlorate to bring the ionic strength up to that of the most concentrated buffered medium.

Reaction media for the formation reactions were prepared by dilution of the required proportions of the stock buffer solution with aqueous hypochlorous acid. Sodium perchlorate was added to bring the ionic strength to the required level.

The procedure for a kinetic run was as follows: For a hydrolysis reaction the appropriate quantity of the hypochlorite was measured into a stoppered silica absorption cell, 10-mm. optical path, containing the correct amount of *tert.*-butanol. The cell, together with a matched twin containing the reaction medium and *tert.*-butanol but no hypochlorite, is placed in the "thermospacer" compartment of a Beckman Model DU Spectrophotometer and kept at a constant temperature by circulating water from a thermostat at 25·2° through this compartment. After addition of the hypochlorite, a standard volume of the reaction medium at the thermostat temperature is pipetted in. The cell contents are mixed by vigorous shaking, and readings of optical density at 2900 Å carried out as often as possible (15-sec. intervals) for fast runs, or at regular longer intervals for the slower runs. For the formation reaction the procedure is only slightly different. The reaction cell is filled with the reaction medium prepared as described above, while the reference matched cell contains the diluted buffer solution, identical with the reaction media but for the absence of hypochlorous acid. The required amount of alcohol is pipetted into each cell and, after shaking, measurements of optical density are begun. At the end of every kinetic run, the whole of the ultra-violet absorption curve between 2100 and 3500 Å was determined in order to check the absence of contamination. The spectrophotometer used in this work was modified slightly to increase its sensitivity. The modifications consisted in replacing the 2000-megohm photocell load resistor by one of 10,000 megohm and using a more sensitive galvanometer arranged potentiometrically to read small differences in current. The pH of the reaction mixtures were then determined by means of a Beckman model H pH meter and the total hypochlorite content measured by iodometric procedure using either the visual end point or the "dead-stop" end point (cf. Stone and Scholten, *Anal. Chem.*, 1952, **24**, 671). Examples of two kinetic runs, taken at random, are presented below.

Formation of tert.-*butyl hypochlorite from hypochlorous acid in aqueous* 1·55M-tert.-*butanolic phosphate buffer solution* [Expt. No. 68(1)].

Buffer concentration = 0·05M; pH = 3·0; μ = 0·10; initial [HOCl] = 9·3 × 10^{-3}M; temp = 25·2°.

Time, min.	10^3D	$10^3k/2{\cdot}3$, $min.^{-1}$	Time, min.	10^3D	$10^3k/2{\cdot}3$, $min.^{-1}$	Time, min.	10^3D	$10^3k/2{\cdot}3$, $min.^{-1}$	Time, min.	10^3D	$10^3k/2{\cdot}3$, $min.^{-1}$
1	237	234	1¾	222	243	2½	212·5	247	3¼	206	257
1¼	230	250	2	219	238	2¾	211	238	4	203	238
1½	225	253	2¼	215	250	3	208	248	∞	195	—

$k = 5{\cdot}64 \pm 0{\cdot}16 \times 10^{-1}$ $min.^{-1}$; $K' = C(\varepsilon_2 - \varepsilon_1)/(C\varepsilon_2 - D_\infty) - 1 = 0{\cdot}72$.

Hydrolysis of tert.-*butyl hypochlorite in* 1·55M-tert.-*butanolic phosphate buffer solution* [Expt. No. 86(2)].

μ = 0·10; buffer concn. = 0·40M; pH = 5·0; initial Bu^tOCl = 100 × 10^{-3}M; temp. = 25·2°.

Time, min.	10^3D	$10^3k/2{\cdot}3$, $min.^{-1}$	Time, min.	10^3D	$10^3k/2{\cdot}3$, $min.^{-1}$	Time, min.	10^3D	$10^3k/2{\cdot}3$, $min.^{-1}$	Time, min.	10^3D	$10^3k/2{\cdot}3$, $min.^{-1}$
¾	142	26·6	1¾	146	28·0	3½	152·5	27·8	8½	166	26·0
1	143	27·0	2¼	148	27·5	4¼	155	27·4	10	170	26·5
1¼	144	27·2	2¾	150	28·0	6	160	26·8	11	173·5	27·9
1½	145	27·2	3¼	151·5	27·4	7¼	163·5	26·8	∞	207	—

$k = 6{\cdot}23 \pm 0{\cdot}13 \times 10^{-2}$ $min.^{-1}$; $K' = C(\varepsilon_2 - \varepsilon_1)/(\varepsilon_2 C - D_\infty) - 1 = 0{\cdot}64$.

The authors thank Prof. E. D. Hughes, F.R.S., for useful comments on the manuscript, and Dr. F. S. Klein for the isotopic analyses.

WEIZMANN INSTITUTE OF SCIENCE, REHOVOTH, ISRAEL. [*Received, September 15th*, 1953.]

Ultra-violet Absorption Spectra of Some Organic Hypohalites.

By M. Anbar and I. Dostrovsky.

[Reprint Order No. 4656.]

The ultra-violet absorption spectra of some derivatives of hypochlorous and hypobromous acids were determined in several organic solvents. The spectra were compared with those of the free acids and halogen monoxides. The spectra of hypochlorous and hypobromous acid were examined in aqueous media over a wide range of hydrogen-ion concentration. No spectrophotometric evidence could be found for the existence of H_2OCl^+ and H_2OBr^+, even in the most acid solutions.

In connection with a study of the mechanisms of reaction of organic hypohalites (preceding paper) the absorption spectra in the range 2050—5000 Å of a number of organic hypohalites, hypohalous acids, and halogen monoxides have been determined. The compounds studied include ethyl hypochlorite and hypobromite, *tert.*-butyl hypochlorite and hypobromite, 3 : 3 : 3-trichloro-1-methylpropyl hypochlorite, acetyl hypochlorite and hypobromite, and hypochlorous and hypobromous acid, in all cases, except for the acids, in carbon tetrachloride solution. The spectra of *tert.*-butyl hypochlorite and of acetyl hypochlorite and hypobromite were also measured in acetic acid and heptane solution. The absorption spectra of hypohalous acids were determined in aqueous solution over a pH range from N-sodium hydroxide to 7·5N-perchloric acid.

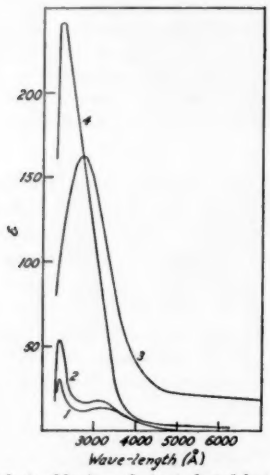
The spectra of hypochlorous and hypobromous acid and of ethyl hypochlorite have been previously investigated. Schaeffer (*Z. physikal. Chem.*, 1919, **93**, 312) reports the absorption spectra of hypochlorous and hypobromous acids in aqueous N-sodium hydroxide and in neutral solution, and that of ethyl hypochlorite in light petroleum–ether. That of aqueous hypochlorous acid was reinvestigated by Fergusson, Slotin, and Style (*Trans. Faraday Soc.*, 1936, **32**, 956). That of hypobromous acid in aqueous N-sodium hydroxide and in aqueous solution has been reported by Farkas and Klein (*J. Chem. Phys.*, 1948, **16**, 886).

The spectra of the hypochlorites and hypobromites in carbon tetrachloride solutions are given in Figs. 1 and 2. The strong band at about 2600 Å is characteristic of the hypochlorite and is present also in the spectrum of chlorine monoxide (Fig. 3). In hypochlorous acid in water the same band appears shifted to 2300 Å (Fig. 4). Substitution of the electron-attracting trichloromethyl group for one of the methyl groups of *tert.*-butyl broadens this band and shifts it to 2880 Å (Fig. 1). In the simple alkyl hypochlorites another weaker maximum is observed around 3100 Å. However, this band is poorly resolved, and with those compounds which show strong absorption in the 2600-Å region the maximum may be absorbed into the base of the bigger peak. Thus, acetyl hypochlorite and 3 : 3 : 3-trichloro-1-methylpropyl hypochlorite show only one strong absorption band, at 2640 Å. The general appearance of the spectra of hypobromites is similar to that of the hypochlorites, but the high peak is shifted to about 2800 Å (cf. Fig. 2), and the other maximum is displaced to 3400 Å. The same maxima appear in hypobromous acid which shows peaks at 2600 and 3200 Å in aqueous solution. No direct comparison of the spectra of hypohalous acids and of hypohalites in the same solvent is possible. However, when due allowance is made for the effect of the change in the solvent, the spectra of hypochlorous and hypobromous acid are seen to be similar to those of their simple alkyl derivatives.

The positions of the bromine monoxide and chlorine monoxide maxima appear to be identical with those of acetyl hypobromite and hypochlorite respectively. This is probably fortuitous, for, although the positions of the maxima are identical, the magnitude of the extinction coefficients is different, that of the halogen monoxides being more than twice that of the corresponding acetyl hypohalites. Another indication that the two spectra belong to different chemical entities is obtained from the fact that on addition of a small quantity of anhydrous acetic acid to a solution of chlorine monoxide in carbon tetrachloride a turbidity is produced which is due to water. When the mixture is clarified by anhydrous sodium sulphate, the spectrum is that of acetyl hypochlorite prepared by

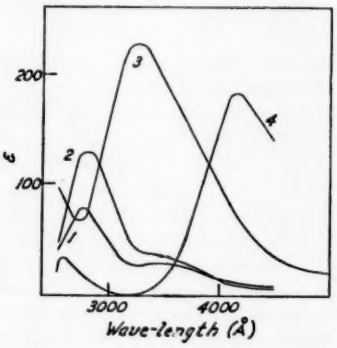
other methods. The reaction taking place is evidently $Cl_2O + 2HOAc \longrightarrow 2ClOAc + H_2O$. We have succeeded in measuring only one band of bromine monoxide, at 3200 Å (in CCl_4) (Fig. 3), corresponding to the short wave-length maximum of a hypobromite. It should

FIG. 1.



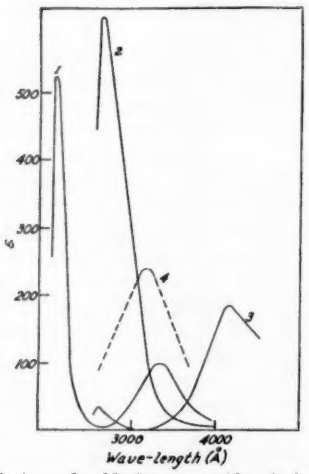
1, *Ethyl hypochlorite*; 2, tert.-*butyl hypochlorite*; 3, 3 : 3 : 3-*trichloro*-1-*methylpropyl hypochlorite*; 4, *acetyl hypochlorite*. (*All in* CCl_4.)

FIG. 2.



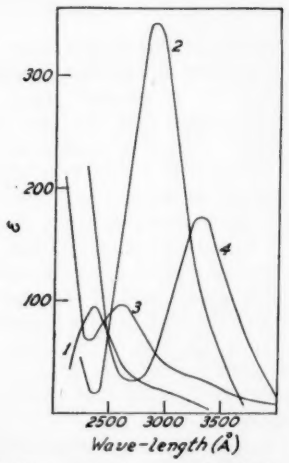
1, *Ethyl hypobromite*; 2, tert.-*butyl hypobromite*; 3, *acetyl hypobromite*; 4, *bromine*. (*All in* CCl_4.)

FIG. 3.



1, *Chlorine*; 2, *chlorine monoxide*; 3, *bromine*; 4, *bromine monoxide*. (*All in* CCl_4.)

FIG. 4.



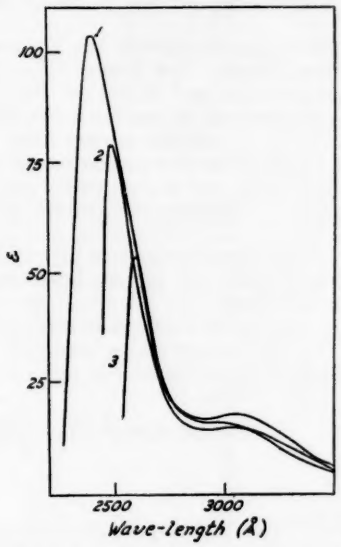
1, *Hypochlorous acid*; 2, *hypochlorite ion*; 3, *hypobromous acid*; 4, *hypobromite ion*. (*All in* H_2O.)

be noted that while the strong maximum at the short wave-length is very sensitive to variations in the solvent (Fig. 5), that at 3100 Å changes only slightly either in intensity or in position.

The spectra of the hypohalite ions differ greatly from those of the un-ionised acids (see Figs. 6 and 4), both hypochlorite and hypobromite ions in aqueous solution showing one strong maximum, at 2920 and 3330 Å respectively. The dissociation constant of

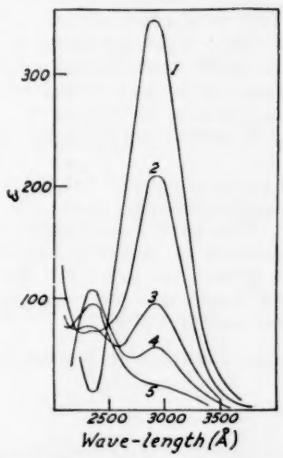
the acid can be determined from the variation in the spectra with change in the acidity of the solution (see Fig. 4). In this way the value of 7·38 for the pK of hypochlorous acid at room temperature was obtained, in good agreement with the values obtained by other methods (*e.g.*, by Shilov and Gladtchikova, *J. Amer. Chem. Soc.*, 1938, **60**, 490; Skrabal and Berger, *Monatsh.*, 1937, **70**, 168). In order to investigate the behaviour of hypohalous acid in strongly acid solution, the extinction curves were determined in aqueous solution containing up to 7·5N-perchloric acid. The curves obtained did not differ from those of the hypohalous acid in weakly acid solutions. This indicates either that the concentration of H_2OCl^+ or H_2OBr^+ is too small to be detected or that the absorption spectra of those species do not differ greatly from those of the unprotonated hypohalous acids.

FIG. 5.



tert.-*Butyl hypochlorite in*: 1, n-*heptane*; 2, *acetic acid*; 3, *carbon tetrachloride*.

FIG. 6.



Hypochlorous acid at:

pH	14·0	7·4	6·8	6·4	1·0
Curve no. ...	1	2	3	4	5

EXPERIMENTAL

Materials.—The solvents used were all of analytical grade. Carbon tetrachloride was purified further by washing it with 10% sulphuric acid and then 10% sodium hydroxide solution and water; after being dried ($CaCl_2$), it was fractionated through a 20-plate column. Anhydrous acetic acid was prepared by adding a slight excess of acetic anhydride to analytical-grade acetic acid, and fractionated through a 12-plate column. *n*-Heptane was purified by shaking it with fuming sulphuric acid and then 10% sodium hydroxide solution and water; after being dried ($CaCl_2$), it was fractionated through a 20-plate column. The lowest limits of measurement with these solvents were 2540 Å for carbon tetrachloride, 2420 Å for acetic acid, and 2040 Å for heptane.

Preparation of Compounds.—Hypochlorous and hypobromous acid were prepared by several methods, generally that of Jakowkin (cf. *Z. physikal. Chem.*, 1899, **29**, 613) based on the action of the halogen on an aqueous suspension of freshly prepared mercuric oxide. The crude hypohalous acid was redistilled at 5 mm. into a trap cooled with liquid nitrogen. Identical spectra were obtained with hypohalous acid prepared by other methods (Shilov and Kanyiaev, *J. Phys. Chem. U.S.S.R.*, 1934, **5**, 655; hydrolysis of *tert.*-butyl hypochlorite or *N*-chlorosuccinamide).

Chlorine monoxide and bromine monoxide in carbon tetrachloride solution were prepared by Schumacher and Townend's method (*Z. physikal. Chem.*, 1933, **20**, *B*, 375). Bromine monoxide could be obtained free from bromine by this method (see Brenshede and Schumacher, *ibid.*, 1935, **29**, *B*, 356; *Z. anorg. Chem.*, 1936, **226**, 370).

tert.-Butyl hypochlorite was prepared by three different methods: (*a*) Chlorine was passed through a cooled alkaline solution of *tert.*-butanol (*Org. Synth.*, 1952, **32**, 20). (*b*) Carbon tetrachloride was shaken with aqueous 0·4N-hypochlorous acid (200 ml.) containing *tert.*-butanol (5 ml.). The carbon tetrachloride layer containing *tert.*-butyl hypochlorite was separated and dried (K_2CO_3). The yield based on the alcohol is quantitative. (*c*) Excess of *tert.*-butanol was added to 0·24N-solution of chlorine monoxide in the solvent (50 ml.), and the mixture dried with anhydrous sodium sulphate. A solution of *tert.*-butyl hypochlorite in carbon tetrachloride was obtained in quantitative yield as shown by the complete disappearance of the spectrum of the monoxide. No difference could be detected in spectra of *tert.*-butyl hypochlorite prepared by the various methods.

Ethyl hypochlorite was prepared by methods similar to (*a*) and (*b*) for *tert.*-butyl hypochlorite.

3 : 3 : 3-Trichloro-1-methylpropyl hypochlorite was prepared by method (*b*) as for *tert.*-butyl hypochlorite.

Acetyl hypochlorite in acetic acid solution was obtained by passing chlorine into a solution either of mercuric acetate in acetic acid (cf. De La Mare, Ketley, and Vernon, *Research*, 1953, **6**, 125) or of silver acetate in acetic acid (cf. Bockenmuller and Hoffmann, *Annalen*, 1935, **519**, 165). A solution in carbon tetrachloride was obtained by (*a*) shaking a solution of chlorine in carbon tetrachloride with excess of silver acetate or mercuric acetate (with the latter a quantitative yield is obtained, whereas with the former it was not possible to obtain a preparation free from chlorine), or (*b*) adding a slight excess of acetic acid to a solution of halogen monoxide in carbon tetrachloride, and drying (Na_2SO_4) (cf. Schutzenberger, *Compt. rend.*, 1861, **52**, 135).

Ethyl hypobromite and *tert.*-butyl hypobromite in carbon tetrachloride were prepared by shaking aqueous hypobromous acid, the corresponding alcohol, and carbon tetrachloride together. The carbon tetrachloride layer was separated and dried.

Measurements of Absorption Spectra.—These were measured in silica cells of 10-mm. optical path with a Beckman model DU Spectrophotometer, modified to increase its sensitivity (cf. Anbar and Dostrovsky, preceding paper). The concentration of hypohalites in solution was determined iodometrically.

WEIZMANN INSTITUTE OF SCIENCE, REHOVOTH, ISRAEL. [*Received, September 15th*, 1953.]

Aromatic Hydrocarbons. Part LXVI. Diperinaphthylene-anthracenes.*

By E. CLAR, W. KELLY, and (in part) J. W. WRIGHT.

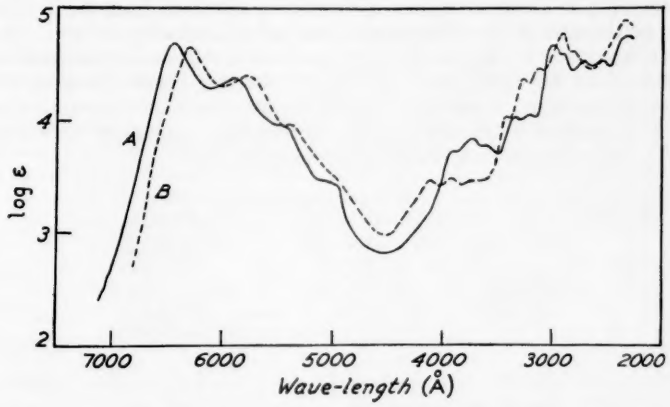
[Reprint Order No. 4737.]

1 : 9-5 : 10- and 1 : 9-4 : 10-Di*peri*naphthyleneanthracene have been prepared by an unambiguous method from 1 : 5- and 1 : 4-dichloroanthraquinone respectively. They show similar properties. Their absorption spectra are compared with quantum mechanical predictions by M. J. S. Dewar.

1 : 5- and 1 : 4-DICHLOROANTHRAQUINONE condense with 1-naphthylmagnesium bromide, to give the diols (I) and (IV) respectively. These are reduced by hydrogen iodide to the corresponding anthracenes, which cyclise smoothly to the hydrocarbons (II) and (V) when heated with potassium hydroxide in quinoline. For (I) ring closure in the β-position of the naphthalene radicals is excluded by the fact that the corresponding dibenzorubicene (Scholl and Meyer, *Ber.*, 1934, **67**, 1229) is completely different from (II). The structure of (II) is thus clear, and the structure (V) follows with almost equal certainty by analogy. The analogy is confirmed in that the hydrocarbons (II) and (V) show similar absorption spectra (Fig. 1). The spectra of their maleic anhydride addition products (III) and (VI) are however quite different (Fig. 2): comparison with the spectrum of benzanthrene shows the aromatic complex dominant in the spectrum of (III) to be most probably that

* Part LXV, *J. Amer. Chem. Soc.*, 1953, **75**, 2667.

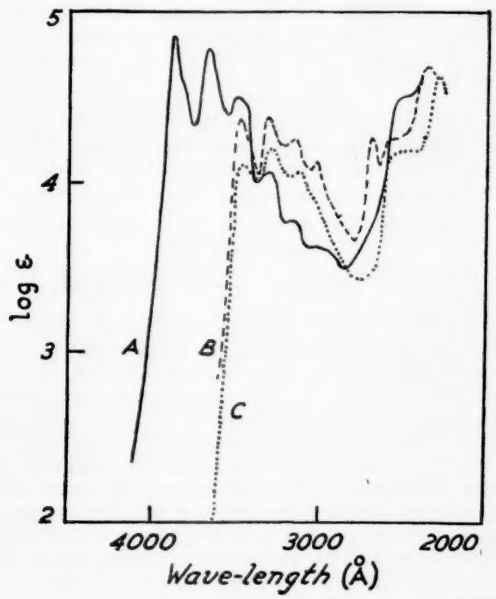
FIG. 1.



A, Absorption spectrum of 1 : 9-4 : 10-*diperinaphthylene anthracene* (V). *Maxima* (Å; *log* ε *in parentheses*): 6435 (4·67), 5890 (4·36), 5440 (3·96), 5030 (3·46); 3920 (3·73), 3740 (3·84); 3360 (4·04), 3220 (4·05), 2980 (4·66) *in benzene*; 2720 (4·54), 2540 (4·52), 3360 (4·74) *in alcohol.*

B, Absorption spectrum of 1 : 9-5 : 10-*diperinaphthylene anthracene* (II). *Maxima*: 6300 (4·64), 5790 (4·40), 5360 (3·96); 4120 (3·47), 3920 (3·47), 3720 (3·47); 3420 (4·02), 3280 (4·36), 3120 (4·44), 2920 (4·76) *in benzene*; 2360 (4·88) *in alcohol.*

FIG. 2.



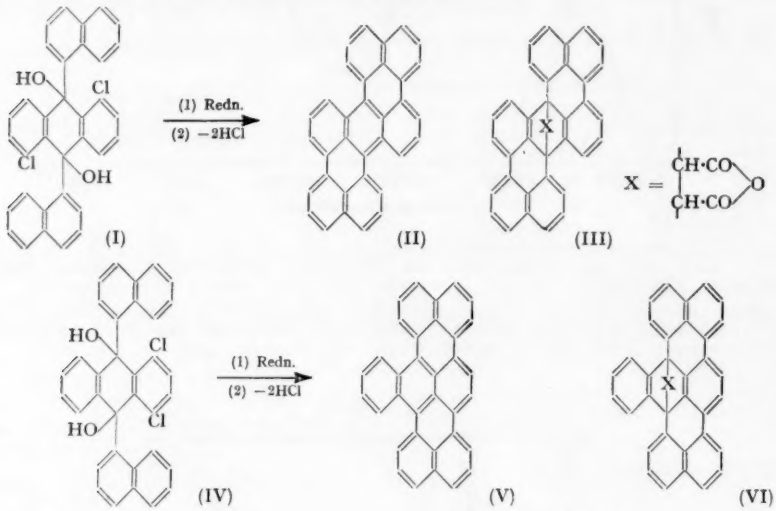
A, Absorption spectrum of the disodium salt from the maleic anhydride adduct (III) *in alcohol. Maxima* (Å; *log* ε *in parentheses*): 3880 (4·84), 3670 (4·78), 3480 (4·50), 3310 (4·06), 3160 (3·76); 2510 (4·46).

B, Disodium salt from the maleic anhydride adduct (VI) *in alcohol. Maxima*: 3465 (4·37), 3290 (4·38), 3140 (4·26), 3020 (4·13); 2680 (4·23); 2380 (4·66).

C, Benzanthrene in alcohol. Maxima: 3440 (4·14), 3290 (4·22), 3120 (4·08); 2500 (4·20); 2280 (4·64).

of benzanthrene; if an analogous addition is assumed for the addition product of V, the dibenzoterphenyl complex is the dominant feature of its spectrum.

The product (V) is identical with a hydrocarbon obtained from 9 : 10-dihydro-9 : 10-di-1′-naphthylanthracene-9 : 10-diol by an aluminium chloride ring closure. This synthesis could give (II) and/or (V). Although preference was first given to the formula (II) (Clar and Guzzi, *Ber.*, 1932, **65**, 1521), later work (J. W. Wright, Thesis, Glasgow, 1949) showed that the same hydrocarbon could be obtained, by a sodium chloride–aluminium chloride melt, from 1 : 4-dichloro-9 : 10-di-1′-naphthylanthracene, and must therefore have the structure (V). The present work confirms this assignment.



The wave-lengths of the first absorption bands for (II) and (V) have been calculated by Dewar (*J.*, 1952, 3539) as 8430 and 6410 Å respectively. The observed values were 6300 and 6435 Å respectively. No other absorption band could be detected in the red as far as 10,000 Å.

Experimental

M. p.s were taken in evacuated capillaries. Microanalyses are by Mr. J. M. L. Cameron and Miss M. W. Christie.

1 : 5-*Dichloro*-9 : 10-*dihydro*-9 : 10-*di*-1′-*naphthylanthracene*-9 : 10-*diol* (I).—A suspension of finely powdered 1 : 5-dichloroanthraquinone (35 g.) in benzene (350 c.c.) was added with stirring during 15 min. to 1-naphthylmagnesium bromide prepared from 1-bromonaphthalene (103 g.) and magnesium (12 g.) in ether (200 c.c.). The temperature was allowed to rise during the addition. 200 c.c. of solvent were distilled from the mixture, which was then heated under reflux on a water-bath for 2 hr., with continuous stirring. The thick suspension was decomposed by pouring it into dilute acetic acid containing ice. Benzene and some naphthalene were removed by steam-distillation. The product was triturated and washed with ether (400 c.c.), digested thoroughly with a large excess of alkaline sodium dithionite solution to remove unchanged starting material, and washed with hot water, a pale fawn solid (38 g.) being obtained. Crystallisation from 1 : 2 : 4-trichlorobenzene gave colourless prisms, m. p. 328—329° (decomp.), of the *diol* (I) (Found: C, 76·5; H, 4·5; Cl, 13·5. $C_{34}H_{22}O_2Cl_2$ requires C, 76·6; H, 4·2; Cl, 13·3%). It gave a transient green colour changing to brown, in concentrated sulphuric acid.

1 : 5-*Dichloro*-9 : 10-*di*-1′-*naphthylanthracene*.—A suspension of the diol (I) (25 g.) in acetic acid (150 c.c.) and hydriodic acid (21 c.c.; 55%) was heated under reflux for 15 min., cooled, filtered, and washed with acetic acid and benzene, to give a yellow product (21 g.) which crystallised from 1 : 2 : 4-trichlorobenzene, yellow prisms, m. p. 338—339°, of 1 : 5-*dichloro*-

9 : 10-*di*-1′-*naphthylanthracene* being obtained (Found : C, 81·9; H, 4·0; Cl, 14·0. $C_{34}H_{20}Cl_2$ requires C, 81·8; H, 4·0; Cl, 14·2%). It was insoluble in concentrated sulphuric acid.

1 : 9-5 : 10-*Di*per*inaphthyleneanthracene* (II).—A mixture of 1 : 5-dichloro-9 : 10-di-1′-naphthylanthracene (2 g.), powdered potassium hydroxide (10 g.), and quinoline (12 c.c.) was heated under reflux for 45 min. The colour of the solution changed through deep red, violet-red, and bluish-violet to blue. The quinoline layer was decanted into dilute hydrochloric acid, and the deep blue precipitate, after being filtered off and washed with hydrochloric acid and water, was sublimed in vacuum at 300—310°/8 $\times$ 10^{-5} mm. Crystallisation of the sublimate (1 g.) from xylene gave deep blue prisms with a coppery sheen, m. p. 333—334°, of 1 : 9-5 : 10-*di*per*inaphthyleneanthracene* (Found : C, 95·8; H, 4·2. $C_{34}H_{18}$ requires C, 95·75; H, 4·25%). When mixed with a sample of the hydrocarbon obtained by Clar and Guzzi (*loc. cit.*), it melted at 288—296°. In concentrated sulphuric acid it gave a green colour which quickly became pinkish-brown. Its solution in xylene was blue with a red fluorescence.

Maleic Anhydride Adduct (III).—The hydrocarbon (II) (40 mg.) and maleic anhydride (30 mg.) were heated under reflux in xylene (20 c.c.) for 5 min.; the solution did not become colourless. During the reaction, the *adduct* crystallised as colourless prisms with a faint bluish tinge, decomp. above 200° to the blue hydrocarbon (Found : C, 87·0; H, 4·0. $C_{38}H_{20}O_3$ requires C, 87·0; H, 3·8%).

1 : 4-*Dichloro*-9 : 10-*dihydro*-9 : 10-*di*-1′-*naphthylanthracene*-9 : 10-*diol* (IV).—This preparation was similar to that of (I), but from 1 : 4-dichloroanthraquinone. Crystallisation from xylene and nitrobenzene gave colourless prisms, m. p. 312—313° (decomp.), of the *diol* (IV) (Found : C, 77·4; H, 4·4. $C_{34}H_{22}O_2Cl_2$ requires C, 76·6; H, 4·2%), which dissolved in concentrated sulphuric acid to a dark greenish-brown solution.

1 : 4-*Dichloro*-9 : 10-*di*-1′-*naphthylanthracene*.—The diol (IV) was reduced as described above for the corresponding 1 : 5-dichloro-compound. The product crystallised from xylene, pale yellow needles, m. p. 341—342°, of 1 : 4-*dichloro*-9 : 10-*di*-1′-*naphthylanthracene* being obtained (Found : C, 81·5; H, 4·5; Cl, 13·9. $C_{34}H_{20}Cl_2$ requires C, 81·8; H, 4·0; Cl, 14·2%). It was insoluble in concentrated sulphuric acid.

1 : 9-4 : 10-*Di*per*inaphthyleneanthracene* (V).—(a) *By ring closure with potassium hydroxide.* The reduced 1 : 4-dichloro-compound was treated with potassium hydroxide and quinoline, as described above, though 20 min. sufficed to effect ring closure. An 83% yield of sublimed 1 : 9-4 : 10-*di*per*inaphthyleneanthracene* (V) was obtained. This crystallised from xylene as dark green-blue prisms or needles, m. p. 348—350° (Found : C, 95·9; H, 4·3. $C_{34}H_{18}$ requires C, 95·75; H, 4·25%). There was no depression of the m. p. on admixture with Clar and Guzzi's hydrocarbon (*loc. cit.*). It dissolved in concentrated sulphuric acid to give a blue-green solution.

(b) *By ring closure with an aluminium chloride–sodium chloride melt.* The reduced 1 : 4-dichloro-compound (1 g.) was added to an aluminium chloride (5 g.)–sodium chloride (1 g.) melt at 110°. After 5 min. at 110—120°, the mixture was poured into dilute hydrochloric acid. The blue-black product, after being washed with hot dilute hydrochloric acid and water and dried, was chromatographed in benzene on alumina. Elution with benzene–light petroleum (b. p. 40—60°) gave a colourless, followed by an orange, band. A third blue-green band (benzene) yielded blue-green chlorine-containing needles, m. p. >360°. A fourth, blue band on elution with benzene gave greenish-blue, glistening needles m. p. 348—350°, identical with the previous sample of (V).

Maleic Anhydride Adduct (VI).—The hydrocarbon (V) was heated with a large excess of maleic anhydride at 150—200°. Crystallisation of the product from a mixture of xylene and acetic anhydride gave colourless prisms of the adduct (VI). It was identical with Clar and Guzzi's adduct (*loc. cit.*).

UNIVERSITY OF GLASGOW.

[*Received, October 20th*, 1953.]

An Electrochemical Study of Salmine Salts.

By C. W. Davies and G. H. Nancollas.

[Reprint Order No. 4764.]

The conductivities at 25° of aqueous solutions of the protamine salmine sulphate and salmine hydrochloride are reported, and an approximate value (87·7 ± 0·7) is derived for the mobility of the salmine cation. The basic groups of salmine are not all of identical strengths, and its electrometric titration curve shows two distinct breaks.

A complete amino-acid analysis of the protamine salmine has been given by Tristram (*Nature*, 1947, **160**, 637), and Mills (*Biochem. J.*, 1952, **50**, 707) has reported closely concordant results. The strongly basic nature of salmine is due to the free guanidine groups of the arginine residues, and Tristram's work points to there being 40 of these in an open-chain polypeptide containing 58 residues in all and having a molecular weight of 8000. A study of the conductivities of some salmine salts seemed likely to be of interest, since salmine occupies an intermediate position between highly charged complex ions such as that studied by James (*Trans. Faraday Soc.*, 1951, **47**, 392) and typical colloids.

Experimental

The conductivity equipment and experimental technique were as described by Davies (*J.*, 1937, 432). All measurements were made at 25° ± 0·01°. Two conductivity cells were used : a Hartley–Barrett quartz cell (cell constant = 0·046280 ± 0·03%), and a hard-glass cell with sealed-in electrodes (cell constant = 0·12251 ± 0·03%). The cells were standardised against potassium chloride solutions of concentrations up to about 1×10^{-3}M by using the interpolation formula (Davies, *loc. cit.*) $\Lambda = 149{\cdot}92 - 93{\cdot}85C^{\frac{1}{2}} + 50C$. Gahl and Greves (*Univ. Calif. Pub. Physiol.*, 1926, **5**, 289) have recommended the use of smooth platinum electrodes for measurements of the conductivity of protein solutions. In the present work, however, platinum-black electrodes were used and gave perfectly reproducible resistance readings.

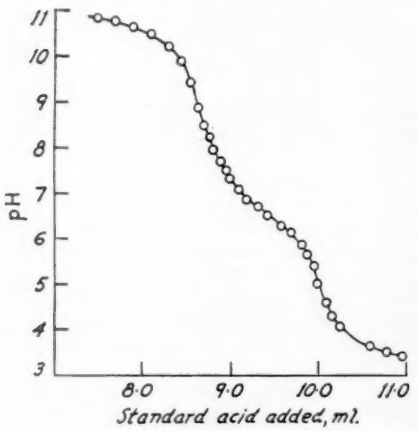


Fig. 1.

Potentiometric titration curve of salmine with hydrochloric acid.

For the measurement of pH, a glass-electrode system was used. The reference electrode was a dipping silver–silver chloride electrode contained in a potassium chloride liquid-junction tube fitted with a ground-glass cap. It was made by Brown's method (*J. Amer. Chem. Soc.*, 1934, **56**, 646). The pH cell was immersed in an oil thermostat at 25° ± 0·01°, and, during runs, was swept free of air with purified nitrogen. A "Cambridge" bench-model pH meter was used, and calibrated with a 0·05M-potassium hydrogen phthalate solution which, at 25°, has a pH of 4·005 (Acree, Hamer, and Pinching, *J. Res. Nat. Bur. Stand.*, 1944, **33**, 287). In order to reduce interference effects, the current to the thermostat was switched off whilst readings were being taken.

Salmine Sulphate.—A commerical sample of salmine sulphate, when titrated conductimetrically with baryta solution, gave an equivalent weight of 1400 which compared very unfavourably with the value 200, determined by Tristram (*loc. cit.*). This indicated a considerable amount of impurity in the sample, probably including nucleic acid with which salmine is combined in the natural state.

The salt was purified by a modification of the methods described by Kossel ("The Protamines and Histones," 1886). The crude salmine sulphate was dissolved in hot water (100 ml. per g. of salt) and, on cooling, the least soluble fraction of the salt separated as a yellow oil. The supernatant liquid was evaporated under reduced pressure to about half its volume and transferred to a separating funnel to collect the main bulk of the salt, again as an oil. This

middle fraction, the purest, was further purified by treatment with a solution of sodium picrate which precipitated the salmine as salmine picrate. The well-washed precipitate was dissolved in an excess of 2N-sulphuric acid, the solution was freed from picric acid by shaking it with toluene, and the salmine sulphate was precipitated by addition of alcohol. Final purification was effected by three times dissolving it in a little hot water and precipitating with absolute alcohol. It was dried by washing it with alcohol, then with ether, and keeping over phosphoric oxide in a vacuum-desiccator. Stock solutions were made up by weight from conductivity water, and, owing to its hygroscopic nature, the dried salt was weighed out in stoppered weighing bottles which were dropped into the stock flasks. The equivalent weight of the purified salmine sulphate, determined gravimetrically by precipitation of the sulphate as barium sulphate, was 231·2.

Salmine Hydrochloride.—A method described in the literature (Kossel, *op. cit.*) for the preparation of salmine hydrochloride involves the addition of the calculated amount of barium chloride to a solution of salmine sulphate. This is not satisfactory for conductivity work, so solutions of salmine hydrochloride were prepared by passing solutions of the purified sulphate through a column of the strongly basic ion-exchange resin Amberlite IRA-400 in the hydroxyl form. The resulting basic solution was converted into that of the hydrochloride by potentiometric titration with hydrochloric acid (glass-electrode). A typical titration curve is shown in Fig. 1. It has two points of inflexion, and the second was taken as that at which complete conversion into salmine hydrochloride occurred. End-points were determined from the data by Kolthoff and Lingane's method (*J. Amer. Chem. Soc.*, 1936, **58**, 1531). The equivalent weight of salmine sulphate calculated for the second end-point was 237. In view of the uncertainty in removing the last traces of free base from the resin column, this agrees well with the gravimetric equivalent.

Conductivity and pH figures for salmine sulphate and hydrochloride in the concentration range 1×10^{-5} to 1×10^{-3} g.-equiv./l. are given in Tables 1—4.

TABLE 1. *Conductivity of salmine sulphate solutions.*

$\kappa_{H_2O} = 2{\cdot}58 \times 10^{-7}\ \Omega^{-1}$.

Expt. No. 1			Expt. No. 1 (corr.)			Expt. No. 2					
10^4C	$10^2C\frac{1}{2}$	Λ	10^4C	$10^2C\frac{1}{2}$	Λ	10^4C	$10^2C\frac{1}{2}$	Λ	10^4C	$10^2C\frac{1}{2}$	Λ
0·08674	0·2945	194·1	0·08354	0·2912	110·1	0·19132	0·4374	101·1	5·1117	2·261	62·20
0·17504	0·4184	196·6	0·14344	0·3787	102·1	0·3610	0·6008	93·74	7·469	2·733	58·16
0·3088	0·555	198·5	0·2499	0·4999	97·54	0·5532	0·7438	88·63	10·045	3·169	55·12
0·7394	0·8599	192·6	0·5884	0·7671	86·92	1·0944	1·0461	80·39	12·455	3·529	53·01
1·8044	1·3433	185·8	1·4374	1·1990	76·90	2·0544	1·433	72·72			
2·9892	1·7290	181·6	2·3866	1·5450	72·01						
6·0581	2·4614	175·5	4·798	2·1910	63·31						

TABLE 2. pH *of salmine sulphate solutions.*

Expt. No. 1						Expt. No. 2					
10^4C	$10^2C\frac{1}{2}$	pH	10^4C	$10^2C\frac{1}{2}$	pH	10^4C	$10^2C\frac{1}{2}$	pH	10^4C	$10^2C\frac{1}{2}$	pH
0·08118	0·2849	5·832	1·2527	1·1193	4·493	0·2948	0·5429	6·070	6·752	2·598	5·800
0·2029	0·4504	5·323	1·9893	1·4105	4·293	0·6834	0·8267	6·013	9·660	3·108	5·768
0·3367	0·5802	5·068	3·038	1·743	4·118	1·3505	1·1620	5·958	12·322	3·510	5·740
0·4244	0·6514	4·953	8·669	2·944	3·590	2·524	1·589	5·898	15·262	3·907	5·727
0·6240	0·7899	4·807				3·828	1·956	5·858			

TABLE 3. *Conductivity of salmine hydrochloride solutions.*

$10^6\kappa_{H_2O} = 0{\cdot}228$ (Expt. 5); 0·205 (Expt. 6).

Expt. No. 5			Expt. No. 6			Expt. No. 6 (corr.)		
10^4C	$10^2C\frac{1}{2}$	Λ	10^4C	$10^2C\frac{1}{2}$	Λ	10^4C	$10^2C\frac{1}{2}$	Λ
0·1118	0·3344	154·0	0·1193	0·3452	163·3	0·1144	0·3401	157·2
0·2411	0·4910	152·2	0·3582	0·5985	157·1	0·3500	0·5916	150·7
0·5209	0·7217	147·6	0·7193	0·8481	152·2	0·7028	0·8383	145·6
0·9622	0·9809	143·6	1·175	1·084	147·9	1·148	1·072	141·4
1·546	1·244	139·0	1·800	1·342	143·8	1·759	1·326	137·4
2·240	1·497	135·2	2·556	1·599	140·2	2·498	1·580	133·7
3·962	1·991	128·7	3·503	1·872	137·1	3·423	1·851	130·3
7·062	2·658	121·7	5·117	2·262	132·4	5·000	2·238	125·7
8·439	2·905	119·5	6·662	2·581	129·3	6·509	2·583	122·4
10·23	3·198	117·2	8·065	2·840	127·1	7·880	2·810	120·2
			9·412	3·068	125·3	9·196	3·040	118·3

TABLE 4. pH *of salmine hydrochloride solutions.*

Expt. No. 6						Expt. No 6 (corr.)					
10^4C	$10^3C^{\frac{1}{2}}$	pH	10^4C	$10^3C^{\frac{1}{2}}$	pH	10^4C	$10^3C^{\frac{1}{2}}$	pH	10^4C	$10^3C^{\frac{1}{2}}$	pH
0·5772	0·7597	5·482	3·843	1·961	4·860	0·5640	0·7510	5·90	3·755	1·940	5·61
1·216	1·103	5·260	5·448	2·334	4·740	1·188	1·090	5·81	5·323	2·310	5·55
2·013	1·419	5·068	7·086	2·662	4·650	1·967	1·407	5·73	6·924	2·630	5·51
3·018	1·737	4·943	9·890	3·145	4·527	2·949	1·719	5·66	9·663	3·110	5·45

RESULTS AND DISCUSSION

The high Λ and low pH values obtained in Expt. 1 (Tables 1 and 2) may be due to two factors. Either the salmine sulphate has a small amount of free sulphuric acid present as an impurity, or considerable hydrolysis takes place. If the effect is due to free acid, then the pH of the solution should vary linearly with log C, and examination of the

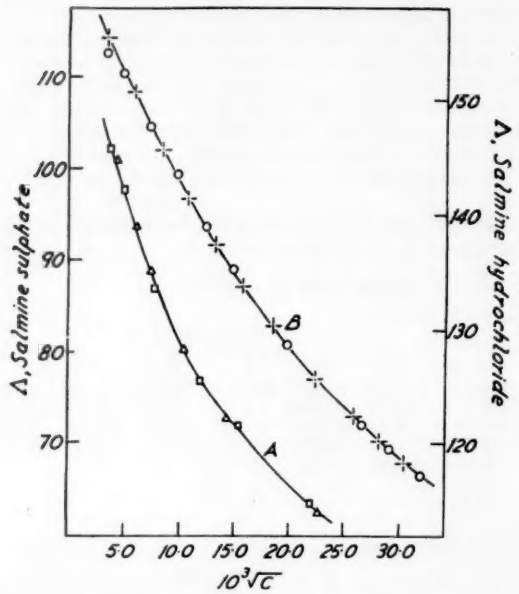


FIG. 2.
Conductivity data at 25°.
A = Salmine sulphate
[□, Expt. 1 (corrected); △, Expt. 2.]
B = Salmine hydrochloride
[+, Expt. 6 (corrected); ○, Expt. 5].

results in Table 2 shows this to be accurately true. The conductivity values were corrected for the free acid in solution by calculating, from the pH measurements, the contribution made by the sulphuric acid to the total specific conductance at each concentration studied. $\Lambda_{H_2SO_4}$ was obtained from the Onsager equation:

$$\Lambda = \Lambda_0 - [1{\cdot}932\ \Lambda_0 q/(1 + \sqrt{q}) + 110{\cdot}7]c^{\frac{1}{2}}$$

where $q = 2\Lambda_0/3(\Lambda_0 + \Lambda_0^{H^+}) = 0{\cdot}3676$. Errors in this approximate Onsager correction will be very small compared with the total conductivity.

Justification of the corrections is provided by the results of Expt. 2. In this, the free acid supposedly present in the salmine sulphate was neutralised with ammonium hydroxide in one step of the purification process. Fig. 2, in which conductivities are plotted against $C^{\frac{1}{2}}$, indicates the excellent agreement between Expt. 2 and Expt. 1 (corrected), confirming that the acidity in Expt. 1 was largely due to free acid.

The pH of the stock solution of salmine hydrochloride used in Expt. 5 was found to be 4·78. This agreed very well with the pH at the equivalence point (4·75, Fig. 1). In Expt. 6, the high Λ and low pH values indicated that excess of acid was present; a linear plot of pH against log C confirmed this. The conductivity data were corrected for the

contribution made by free hydrochloric acid to the total specific conductance at each point, Λ_{HCl} being calculated from the Onsager equation:

$$\Lambda = \Lambda_0 - 157{\cdot}68C_{HCl}^{\frac{1}{2}}$$

Fig. 2, in which conductivities are plotted against $C^{\frac{1}{2}}$, indicates the good agreement between Expt. 5 and Expt. 6 (corrected) even though different samples of purified salmine sulphate were used in the preparation of their solutions.

The equivalent conductances of the salts are of the same magnitudes as those of simple electrolytes, but compared with these show, as might be expected, a much more rapid decrease with rising concentration. There is no method of estimating how much of this is due to ion-association and how much to normal inter-ionic effects, but for the hydrochloride it seems likely that the latter could account for the greater part of the decrease, and that ion-association is not of great importance at the high dilutions studied. In one

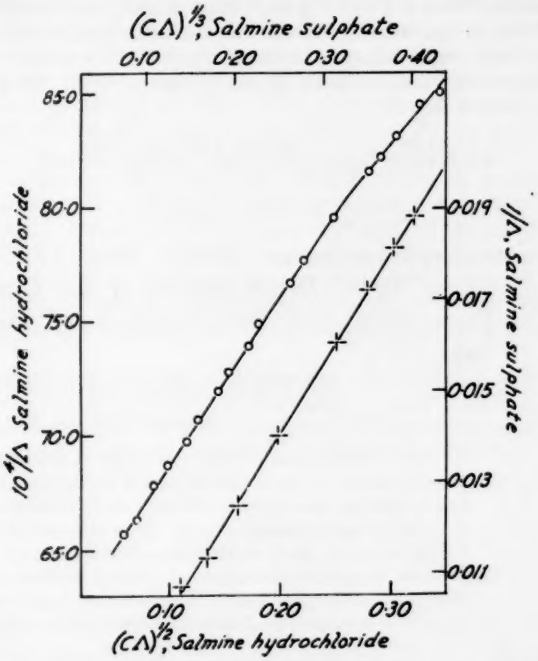


FIG. 3.

Conductivity data plotted according to Storch's equation.

○, Salmine hydrochloride;
+, salmine sulphate.

conductimetric experiment the acetate was formed from the hydrochloride ($C = 0{\cdot}001$) by titration with silver acetate; the conductivity change corresponded with the difference in mobilities of the chloride and acetate ions, so if ion-association occurs in the hydrochloride solutions it does so to the same extent in the acetate.

Below 0·0002N the hydrochloride curve is approximately linear with respect to $C^{\frac{1}{2}}$, and an extrapolation on this basis gives the rough value $\Lambda_0 = 163$. Gahl, Greenberg, and Schmidt (*Univ. Calif. Pub. Physiol.*, 1926, **5**, 307) and Hiyamoto and Schmidt (*J. Biol. Chem.*, 1933, **9**, 335) have found that satisfactory extrapolations are obtained with some salts of proteins when the data are plotted in accordance with Storch's equation (*Z. physikal. Chem.*, 1896, **19**, 13). A similar method is applied to our data in Fig. 3, where $1/\Lambda$ is plotted against $(\Lambda C)^{1/n}$, n having the value 2 for the hydrochloride and 3 for the sulphate. Good straight lines are obtained, leading to $\Lambda_0 = 164{\cdot}6$ for salmine hydrochloride and $\Lambda_0 = 167$ for the sulphate; the latter is rather less accurate owing to the longer extrapolation required for its determination.

If the mobilities of the chloride (76·3) and sulphate (80·0) ions are deducted, that of the fully ionised salmine cation becomes 88·3 from the hydrochloride, and 87 from the sulphate data. The agreement is satisfactory in view of the uncertainties of the extrapolations.

The existence of two end-points (Fig. 1) when basic salmine is titrated against hydrochloric acid is interesting. The effect was found with purified salmine from two different sources, and also with a pure sample kindly given by Dr. Tristram. The end-points are slightly sharpened by carrying out the titration in 0·1N-potassium chloride. The effect is not due to contamination by carbon dioxide, as other experiments with a column of Amberlite-400 have shown (Davies and Nancollas, *Nature*, 1950, **165**, 237). From the titration curves the ratio of hydrogen bound at the first point of inflection to that bound at the second was 0·86 in Expt. 5 and 0·84 in Expt. 6.

If there are 40 basic groups in salmine and all are neutralised at the second end-point, only 33 or 34 have reacted at the first point of inflection. This seems to show that in salmine there are 6 or 7 groups more weakly basic than the others. It has been suggested (Tristram, personal communication) that in salmine the hydroxyl groups of the six serine residues might influence the basic character of a similar number of guanidine groups. This suggestion must remain a tentative one, however, until the structure of salmine is known in greater detail.

THE EDWARD DAVIES CHEMICAL LABORATORIES,
UNIVERSITY COLLEGE OF WALES, ABERYSTWYTH. [*Received, November 2nd*, 1953.]

Quaternary Ammonium Salts. Part IV. Hydrolysis of the Nitrile Group before Decomposition of the Quaternary Ammonium Group. Preparation and Decomposition of Some Quaternary Ammonium Salts.*

By WADIE TADROS and ALFY BADIE SAKLA.

[Reprint Order No. 4782.]

Ethanolic sodium ethoxide hydrolysed the nitrile group of *p*-cyanophenyltrimethylammonium iodide before it decomposed the ammonium group; the amide formed then gave *p*-ethoxy- and *p*-dimethylamino-benzamide. *o*- and *p*-Dimethylaminobenzoic acid gave the quaternary salts with methyl iodide only in methyl alcohol. Decomposition of 4-dimethylaminobenzophenone-4′-trimethylammonium iodide with alcoholic sodium methoxide or ethoxide gave 4-dimethylamino-4′-methoxy- or -ethoxy-benzophenone, Michler's ketone, and 4-dimethylamino-4′-hydroxybenzophenone.

WHEN *p*-cyanophenyltrimethylammonium iodide was boiled with ethanolic sodium ethoxide for 15 min., the nitrile was hydrolysed to the amide group before degradation of the quaternary ammonium group occurred. The nitrile group behaved therefore like the formyl, nitro-, methoxy- and ethoxycarbonyl groups (Parts II and III *). On prolonged boiling (2 hr.) both the nitrile and the amide yielded *p*-dimethylaminobenzamide, *p*-ethoxybenzamide, and a trace of *p*-dimethylaminobenzoic acid. The formation of *p*-ethoxybenzamide may be attributed to the electron-attracting properties of the carbamoyl group. It was noteworthy that whereas the nitrile group in the *p*-cyanoammonium salt was readily hydrolysed, *p*-dimethylaminobenzonitrile was only hydrolysed after 6—8 hr.' refluxing (cf. *p*-dimethylaminobenzaldehyde which does not readily undergo the Cannizzaro reaction, in contrast to the quaternary salt, Part II).

When *o*-dimethylaminobenzoic acid and methyl iodide were heated on the water-bath for 3 hr. or left for 2 days at room temperature, methyl *o*-dimethylaminobenzoate hydriodide was obtained, but the *p*-dimethylamino-acid was recovered unchanged even after

* Parts I—III, *J.*, 1949, 3337; 1951, 1890; 1953, 189.

much longer treatment. The two electrons of the tertiary nitrogen atom were not apparently available for the addition of methyl iodide (see Watson, " Modern Theories of Organic Chemistry," Oxford Univ. Press, 1941, p. 252) under the experimental conditions cited. The formation of methyl *o*-dimethylaminobenzoate hydriodide may be attributed to the betaine structure $^{+}NHMe_2 \cdot C_6H_4 \cdot CO_2^{-}$ (Ley and Ulrich, *Ber.*, 1909, **42**, 3440; Ley and Engelhardt, *Z. physikal. Chem.*, 1910, **74**, 1; Hünecke, *Ber.*, 1927, **60**, 1451; Devoto, *Chem. Zentr.*, 1934, II, 3753), the methyl radical adding itself to the negatively charged CO_2^{-} group. Ley and Ulrich gave, however, a structure which in the light of electronic theory would represent chelation between the carboxyl-hydrogen and the nitrogen atom through the unshared electrons. The failure to obtain the corresponding salt or the quaternary ammonium compound in case of the *p*-isomer may (with reservation) find explanation in the quinonoid structure $^{+}NMe_2 \cdot C_6H_4 \cdot C(OH) \cdot O^{-}$ suggested by Kumler (*J. Amer. Chem. Soc.*, 1946, **68**, 1184) for this acid and related compounds. As already pointed out by Edsall and Wyman (*ibid.*, 1935, **57**, 1964) *o*- and *p*-dimethylaminobenzoic acid exhibit markedly different properties (melting points, solubilities, solvents, etc.). However, when either acid was refluxed with an excess of methyl iodide in solution in methyl alcohol, the corresponding quaternary salt was obtained. On prolonged boiling, the methyl ester of the *p*-compound was formed (contrast the hydrolysis of the ester group before degradation of the quaternary group; Part III). It is therefore reasonable to assume that the two acids may exist (at least at the time of the reaction) in the uncharged form when in solution in methyl alcohol, the unshared electrons thus becoming available for the addition of methyl iodide. Kuhn and Brydówna (*Ber.*, 1937, **70**, 1333), by passing diazomethane through an aqueous solution of *o*-dimethylaminobenzoic acid, obtained 18% of *o*-benzobetaine and 70% of methyl *o*-dimethylaminobenzoate, but 97% of the methyl ester was formed in ether. Edsall and Wyman (*loc. cit.*) noted that *o*-dimethylaminobenzoic acid in solvents such as water, alcohol–water, and benzene existed predominantly in the zwitterion form. *m*-Dimethylaminobenzoic, *p*-dimethylaminocinnamic, and β-*p*-dimethylaminophenylpropionic acid readily added methyl iodide on the water-bath or at room temperature (2 days).

On decomposition of 2-methoxycarbonyl-1-phenylethylene-*p*-trimethylammonium iodide with methanolic sodium methoxide the ester group was cleaved before the quaternary group was affected. Decomposition of 4-dimethylaminobenzophenone-4′-trimethylammonium iodide gave 3 fractions which were separated as reported in Part I.

Experimental

Quaternary Iodides.—These were obtained in most cases in almost theoretical yield at room temperature (2 days) or on the water-bath (6 hr.) from the base (1 g.) and an excess of methyl iodide (25 g.) alone or in presence of methyl alcohol (25 c.c.). The iodides from *o*- and *p*-dimethylaminobenzoic acid were formed only in presence of the solvent. *p*-Carboxyphenyltrimethylammonium iodide, m. p. 238°, showing no depression on admixture with an authentic sample (Zaki and Tadros, *J.*, 1941, 562), was obtained after 6 hr.' refluxing, but on prolonged boiling (32 hr.) the carboxyl group was esterified (the same result being obtained on prolonged boiling of a mixture of *p*-carboxyphenyltrimethylammonium iodide and methyl iodide in methanol), and *p*-methoxycarbonylphenyltrimethylammonium iodide, m. p. and mixed m. p. 170° (Part III), was formed.

Methyl *o*-dimethylaminobenzoate hydriodide, m. p. and mixed m. p. 163° (Willstätter and Kahn, *Ber.*, 1904, **37**, 401), was obtained when *o*-dimethylaminobenzoic acid and an excess of methyl iodide were refluxed for 3 hr. or left for 2 days at room temperature.

The iodides were recrystallised from alcohol or alcohol–ether from which they separated as colourless or pale yellow crystals. The picrates were prepared from the iodides.

Decomposition of Quaternary Salts.—When 4-dimethylaminobenzophenone-4′-trimethylammonium iodide (4·1 g., 1 mol.) and methanolic or ethanolic sodium methoxide or ethoxide (sodium, 0·35 g., 1·5 atoms; alcohol, 25 c.c.) had been refluxed for 3 hr., three products were separated as follows: Alcohol was distilled off and the residue was treated with hydrochloric acid (1 : 1); to the clear solution 5% aqueous sodium hydroxide was added drop by drop until a precipitate (20—25%) of 4-dimethylamino-4′-methoxy- (m. p. 132°) or -ethoxy-benzophenone (m. p. 103°) separated (no depression on admixture with authentic samples, Part I). The

filtrate (which was still acid) was made alkaline; the resulting precipitate was recrystallised from alcohol and proved by m. p. and mixed m. p. to be Michler's ketone (60—65%). Acidification of the alkaline filtrate by acetic acid precipitated a small amount of 4-dimethylamino-4′-hydroxybenzophenone, m. p. and mixed m. p. 199—200° (Part I).

p-Carbamoylphenyltrimethylammonium iodide (1·51 g., 1 mol.) and ethanolic sodium ethoxide (sodium 0·23 g., 2 atoms; in ethyl alcohol, 25 c.c.), treated as above, gave 3 fractions: *p*-ethoxybenzamide (35—40%), m. p. and mixed m. p. 202° (Gattermann, *Annalen*, 1888, **244**, 29); *p*-dimethylaminobenzamide (40—45%), m. p. and mixed m. p. 206° (Bayer and Co., G.P. 77,329; Friedländer, Vol. IV, p. 173); and *p*-dimethylaminobenzoic acid, m. p. and mixed m. p. 234° showing no depression on admixture with an authentic sample (Zaki and Tadros, *loc. cit.*).

Hydrolysis of the Nitrile Group before Decomposition of the Quaternary Ammonium Group.—*p*-Cyanophenyltrimethylammonium iodide (1·44 g., 1 mol.) and ethanolic sodium ethoxide (sodium, 0·23 g., 2 atoms; in alcohol, 25 c.c.) were refluxed for 15 min. and alcohol was distilled off; the picrate obtained from the residue was *p*-carbamoylphenyltrimethylammonium picrate,

Salt	M. p.	Found (%) C	H	N	Hal	Formula	Required (%) C	H	N	Hal
Substituted phenyltrimethylammonium salts, R·C$_6$H$_4$·NMe$_3$}X.										
R = *p*-CN.										
Iodide	181°	41·6	4·8	9·4	43·8	$C_{10}H_{13}N_2I$	41·7	4·5	9·7	44·1
Picrate	152	48·9	3·9	17·5	—	$C_{16}H_{15}O_7N_5$	49·4	3·9	18·0	—
R = *p*-CO·NH$_2$.										
Iodide	203—204	39·3	5·0	8·8	41·2	$C_{10}H_{15}ON_2I$	39·2	4·9	9·2	41·5
Picrate	237	47·5	4·3	17·6	—	$C_{16}H_{17}O_8N_5$	47·2	4·2	17·2	—
R = *p*-CO$_2$H.										
Iodide[a]	160—161	—	—	4·3	40·8	$C_{10}H_{14}O_2NI$	—	—	4·6	41·4
R = *m*-CO$_2$H.										
Chloride[b] ...	207	—	—	—	15·9	$C_{10}H_{14}O_2NCl$	—	—	—	16·4
Iodide[c]	204	38·9	4·4	4·8	40·8	$C_{10}H_{14}O_2NI$	39·1	4·6	4·6	41·4
R = *o*-CO$_2$Me.										
Picrate[d]	128—130	48·2	4·2	13·7	—	$C_{17}H_{18}O_9N_4$	48·3	4·3	13·3	—
R = *m*-CO$_2$Me.										
Picrate[d]	166	48·1	4·2	12·8	—	$C_{17}H_{18}O_9N_4$	48·3	4·3	13·3	—
2-Carboxy-1-phenylethane-p-trimethylammonium Salts.										
Iodide	206—208	42·8	5·6	4·2	38·3	$C_{12}H_{18}O_2NI$	43·0	5·4	4·2	37·9
Picrate	208—210	49·4	4·9	12·6	—	$C_{18}H_{20}O_9N_4$	49·5	4·6	12·8	—
2-Carboxy-1-phenylethylene-p-trimethylammonium Salts.										
Iodide[e]	210	43·2	4·8	4·1	38·0	$C_{12}H_{16}O_2NI$	43·2	4·8	4·2	38·1
Picrate	228—230	49·9	4·1	12·7	—	$C_{18}H_{18}O_9N_4$	49·8	4·1	12·9	—
2-Methoxycarbonyl-1-phenylethylene-p-trimethylammonium Salts.										
Picrate[f]	187—189	51·7	4·3	12·9	—	$C_{19}H_{20}O_9N_4$	50·9	4·5	12·5	—
4-Dimethylaminobenzophenone-4′-trimethylammonium Salts.										
Iodide[g]	182	53·2	5·8	7·0	31·4	$C_{18}H_{23}ON_2I$	52·7	5·6	6·8	31·0
Picrate[h]	197—198	56·1	4·9	13·2	—	$C_{24}H_{25}O_8N_5$	56·4	4·9	13·7	—

[a] Willstätter and Kahn (*loc. cit.*) gave m. p. 138° and 1 mol. of water of crystallisation. The m. p. was depressed on admixture with methyl *o*-dimethylaminobenzoate hydriodide. [b] Obtained by treatment of *m*-methoxycarbonylphenyltrimethylammonium picrate with concentrated hydrochloric acid, filtration from picric acid, washing with benzene–ether until free from picric acid, and then evaporation on the water-bath. The residue crystallised from alcohol–ether. Cumming (*Proc. Roy. Soc.*, 1907, *A*, **78**, 109), gave m. p. 192°. [c] Also obtained from the chloride by addition of aqueous potassium iodide. Cumming gave m. p. 180°. [d] Obtained from the iodides with m. p. 153° and 220—221° respectively (Willstätter and Kahn, *loc. cit.*). [e] Pfeiffer and Haeflin (*Ber.*, 1922, **55**, 1769) obtained this by heating the acid with methyl iodide for 30 hr. in a sealed tube and by addition of hydriodic acid to the betaine. During the addition of methyl iodide to *p*-dimethylaminocinnamic acid (m. p. 216°; Pandya and Sharma, *J. Indian Chem. Soc.*, 1946, **23**, 137) a part of the acid was recovered but had m. p. 235°. It crystallised from alcohol as yellow crystals (Found: C, 68·8; H, 6·5; N, 7·5. Calc. for $C_{11}H_{13}O_2N$: C, 69·1; H, 6·8; N, 7·3%); the following m. p.s have been recorded: 216° (Weil, *Chem. Zentr.*, 1908, II, 1924; Dutt, *ibid.*, 1925, II, 1852; Pandya and Sharma, *loc. cit.*); 220° (Pfeiffer and Haeflin, *loc. cit.*); 225° (Shoppee, *J.*, 1930, 968). [f] Obtained from the iodide, m. p. 186° (Pfeiffer and Haeflin, *loc. cit.*). [g] Refluxing was for 2 hr. only. Addition to both *p*-dimethylamino-groups took place on refluxing of Michler's ketone with methyl iodide in methanol for 20 hr. and not for 2 hr. as previously stated (Tadros and Latif, *loc. cit.*). [h] Reddish-brown; other picrates were yellow.

m. p. and mixed m. p. 237°. Refluxing the mixture for 2 hr. gave *p*-ethoxybenzamide and *p*-dimethylamino-benzamide and -benzoic acid.

Hydrolysis of the Ester Group before Decomposition of the Quaternary Ammonium Group.—Methanolic sodium methoxide (sodium, 0·17 g., 1·25 atoms; methanol, 20 c.c.) containing 2-methoxycarbonyl-1-phenylethylene-*p*-trimethylammonium iodide (1·75 g., 1 mol.) was left at 25—30°. A sample was daily left to evaporate at room temperature and the residue converted into the picrate. The picrate obtained after 4 days had m. p. 228—230° alone or when mixed with 2-carboxy-1-phenylethylene-*p*-trimethylammonium picrate.

p-Dimethylaminobenzamide.—This was also obtained on refluxing, for 6—8 hr., of *p*-dimethylaminobenzonitrile (3 g., 1 mol.) and ethanolic sodium ethoxide (sodium, 0·7 g., 1·5 atoms; ethyl alcohol, 30 c.c.). It separated from water and had m. p. and mixed m. p. 206°.

CHEMISTRY DEPARTMENT, FACULTY OF SCIENCE,
CAIRO UNIVERSITY, EGYPT.

[*Received, November 10th,* 1953.]

The Preparation and Some Reactions of Nitryl Fluoride.

By E. E. AYNSLEY, G. HETHERINGTON, and P. L. ROBINSON.

[Reprint Order No. 4795.]

A new and simple method of preparing nitryl fluoride, NO_2F, in quantity is described. It is obtained in almost quantitative yield from sodium nitrite by the action of fluorine. The reactions of the compound with many elements and with some non-metallic fluorides and oxides are detailed. It is shown that certain of these reactions lead to new compounds: dinitronium hexafluorogermanate, and nitronium pentafluoroselenite, pentafluorotellurite, and hexafluoroiodate have been prepared.

ALTHOUGH Moissan and Lebeau (*Compt. rend.*, 1905, **140**, 1621) claimed to have prepared nitryl fluoride, NO_2F, and the compound has been the subject of a number of communications, there is apparently no report of a simple method for its preparation in quantity. Moissan and Lebeau thought they obtained the material as the result of the spontaneous combustion of nitric oxide and fluorine; but as they also mentioned (*ibid.*, p. 1573) that fluorine did not react with nitrogen peroxide, what they actually had is open to doubt. Ruff, Menzel, and Neumann (*Z. anorg. Chem.*, 1932, **208**, 293) prepared nitryl fluoride from fluorine and nitrogen peroxide, and the qualitative reactions of their preparation differed so greatly from those given by Moissan and Lebeau that they concluded that the earlier workers were really handling a mixture of nitrosyl fluoride (m. p. −132·5°, b. p. −59·9°) and fluorine. This method of preparation does not give a pure product; and, in order to reduce contamination by silicon, Faloon and Kenna (*J. Amer. Chem. Soc.*, 1951, **73**, 2937) used a lower temperature and treated nitrogen peroxide, liquefied in a Fluorothene vessel, with fluorine. In a further attempt to avoid impurity Schmeisser and Elisher (*Z. Naturforsch.*, 1952, **7**, *b*, 583) passed a stream of nitryl chloride over silver fluoride in a platinum tube at 240°, but obtained only a 5% conversion.

Previous workers differ about the behaviour of nitryl fluoride towards glass. We have found the attack on glass at room temperature to be so slow as to be negligible in the times required for an experiment, but at higher temperatures it is appreciable Faloon and Kenna (*loc. cit.*) stated that nitryl fluoride in a glass vessel becomes contaminated with silicon tetrafluoride, but this is unlikely since, as we show below, silicon tetrafluoride combines with nitryl fluoride to form the white, solid dinitronium hexafluorosilicate which is insoluble in nitryl fluoride.

We have found that fluorine reacts with slightly warm, dry sodium nitrite to give an almost quantitative conversion of the nitrogen into nitryl fluoride, and that since this reaction can be carried out in glass, it forms the most convenient means of preparing the compound. We have made 50 g. per run but this amount could be increased indefinitely

by using more nitrite, always provided the temperature is controlled by adjusting the fluorine flow. The reaction may be formally represented by the successive stages

$$2NaNO_2 + F_2 \longrightarrow 2NaF + 2NO_2$$
$$2NO_2 + F_2 \longrightarrow 2NO_2F$$

but its quantitative character suggests that the sequence is a rapid one and that it probably takes place on the surface of the reaction solid and may possibly be, in the main, a single reaction. The relatively low temperature involved makes the use of glass apparatus possible, and fractionation in a vacuum readily rids the product of the excess of fluorine and traces of nitrogen peroxide whichare condensed with it. Thus treated, nitryl fluoride is a colourless liquid freezing to a white solid.

Reactions of Nitryl Fluoride with Elements.—(*a*) *Metals.* According to their behaviour with nitryl fluoride, metals fall into three groups: (i) those which form an oxide and a fluoride, (ii) those which form an oxyfluoride, and (iii) those which do not react below about 300°.

The first group is by far the largest; and the fact that the gases issuing from the reaction show, on condensation, the blue colour of dinitrogen trioxide indicates that the reaction takes place in at least two stages:

$$M + 2NO_2F \longrightarrow MF_2 + 2NO_2$$
$$M + NO_2 \longrightarrow MO + NO$$
$$NO_2 + NO \longrightarrow N_2O_3$$

The metals chromium, molybdenum, tungsten, and uranium constitute the second group. The oxides of these metals react with nitryl fluoride to give the oxyfluorides. This suggests consecutive reactions involving formation of oxide and leading to the overall result represented by $M + 2NO_2F \longrightarrow MO_2F_2 + 2NO$, provided the temperature is kept below a certain maximum. Above that point oxides and fluorides are formed and the oxyfluoride itself is decomposed.

Examples of the third group are beryllium, magnesium, calcium, and gold.

(*b*) *Non-metals.* So many of these react with nitryl fluoride to give nitronium salts as to make the reaction almost a general method of preparation. Exceptions are bromine and tellurium. The compounds we have prepared are nitronium tetrafluoroborate, $(NO_2)BF_4$; dinitronium hexafluoro-silicate, $(NO_2)_2SiF_6$, and -germanate, $(NO_2)_2GeF_6$; nitronium hexafluorometa-phosphate, -arsenate, and -antimonate, $(NO_2)PF_6$, etc.; nitronium pentafluoroselenite, $(NO_2)SeF_5$, and hexafluoroiodate, $(NO_2)IF_6$. There seems little doubt that the fluoride is first formed and that this reacts with the appropriate number of molecules of nitryl fluoride; *e.g.*,

$$Si + 4NO_2F \longrightarrow SiF_4 + 4NO_2$$
$$SiF_4 + 2NO_2F \longrightarrow (NO_2)_2SiF_6$$

since we have shown that the fluorides combine thus with nitryl fluoride. Several of these nitronium compounds have been prepared previously by other methods which may well have involved nitryl fluoride as the active agent. Thus Woolf and Emeléus (*J.*, 1950, 1050) obtained $(NO_2)BF_4$, $(NO_2)PF_6$, $(NO_2)AsF_6$, and $(NO_2)SbF_6$ by the action of nitrogen peroxide together with bromine trifluoride on a suitable compound of the non-metal; and Schmeisser and Elisher (*loc. cit.*) made $(NO_2)BF_4$ and $(NO_2)_2SiF_6$ by adding a mixture of anhydrous hydrofluoric acid and the appropriate fluoride to a solution of dinitrogen pentoxide in nitromethane.

The distribution of known nitronium fluoro-compounds in relation to the Periodic Table is set out below.

Gp. I	Gp. II	Gp. III	Gp. IV	Gp. V	Gp. VI	Gp. VII
		$(NO_2)BF_4$				
			$(NO_2)_2SiF_6$	$(NO_2)PF_6$		
			$(NO_2)_2GeF_6$	$(NO_2)AsF_6$	$(NO_2)SeF_5$	$[(NO_2)BrF_4]$
			$(NO_2)_2SnF_6$	$(NO_2)SbF_6$	$[(NO_2)TeF_5]$	$(NO_2)IF_6$
$(NO_2)AuF_4$						

Two of the compounds, shown in square brackets, are of special interest. The tellurium compound has been made, not from the element but from the dioxide, TeO_2, which (unlike the trioxide) reacts readily with nitryl fluoride. The nitronium fluoroselenite can also be made in this way as well as from the element. The reaction of nitryl fluoride with elementary tellurium is being further investigated because of the anomalous results obtained under what appear to be identical conditions (see p. 1123).

When nitryl fluoride is bubbled through bromine trifluoride the liquid becomes yellow and viscous. We have not been able to separate a solid by cooling, but we believe the material contains $(NO_2)BrF_4$, the unstable base first postulated by Woolf and Emeléus (*loc. cit.*). The yellow colour is doubtless due to the nitronium ion. Incidentally, the same colour is observed when selenium tetrafluoride and iodine pentafluoride are severally treated with nitryl fluoride. The difficulty of isolating $(NO_2)BrF_4$ is understandable in view of the properties of th- nitronium hexafluoroiodate; this exhibits a high dissociation pressure even at room temperature, but is stable enough at lower temperatures. It is hydrolysed by water almost quantitatively according to the equation $(NO_2)IF_6 + 4H_2O = HNO_3 + HIO_3 + 6HF$, there being no more than a trace of free iodine in the final solution.

Experimental

Preparation of Nitryl Fluoride.—This was conveniently prepared by passing a stream of fluorine (about 4 g./hr.), diluted with nitrogen (1 : 1 by vol.), over sodium nitrite (50 g.), dried by heating to 140° before charging and then flamed out in a vacuum in the glass reaction tube. The optimum concentration of fluorine depends upon the amount and distribution of the nitrite; if it is too great a yellow flame appears—probably of nitrogen peroxide burning in fluorine—and there is much attack on the glass. The gaseous product, which consisted of nitryl fluoride contaminated with a little nitrogen peroxide and the excess of fluorine, was condensed in a trap by means of liquid air and fractionated in a vacuum to free it from fluorine and nitrogen peroxide (Found: N, 21·2; F, 29·1%; *M*, 64·6. Calc. for NO_2F: N, 21·5; F, 29·2%; *M*, 65). The colourless liquid boiled between −73° and −72° under atmospheric pressure, and at *ca.* −160° froze to a white solid.

Reaction of Nitryl Fluoride with Elements.—In the case of solids, nitryl fluoride was passed over the element spread in a glass tube, and, when necessary, heat was applied to start the reaction. The solid residue, except where otherwise stated, was examined by qualitative chemical tests and *X*-ray. *X*-Ray powder photographs were taken with use of Co-$K\alpha$ radiation, the samples being mounted in Pyrex capillaries. In the case of potassium, in addition to the spectrum of potassium fluoride, the *X*-ray evidence included lines which could be ascribed to potassium dioxide, KO_2, and the yellow colour of the solid was in keeping with this. Qualitatively, the material reacted with water, showed strong oxidising properties, and gave evidence of a peroxide. The presence of some of the peroxide, K_2O_2, is not excluded. Again the traces of the highest oxide, mentioned in connection with phosphorus, arsenic, and antimony, were all displayed in the *X*-ray photographs and established by qualitative chemical tests. In every instance blue dinitrogen trioxide was seen in the condensate, indicating a reduction of nitrogen peroxide consequent on oxide formation. Data for the mercury fluorides do not appear in the S.M.T. Index but the greenish colour and the qualitative reactions all pointed to the material's being mercurous fluoride.

The volatile products were condensed or frozen in traps and examined qualitatively.

The results tabulated call for remarks on three elements only. Bismuth formed neither oxide nor nitronium compound: the white solid contained neither BiF_3 nor Bi_2O_3, and qualitative tests showed the presence of fluoride and the absence of nitrogen. On the other hand, uranium which first glowed white-hot produced a sublimate of green uranium tetrafluoride. If the current of nitryl fluoride was then stopped, the original solid was found to have increased many times in bulk and become black. When the reaction was started again, this solid glowed red and the greyish final product consisted mainly of uranyl fluoride with a little U_3O_8. Provided the reaction temperature was kept below 300° the oxyfluoride was formed from either metal or oxide.

Tellurium behaves peculiarly; the reaction which started spontaneously at room temperature and evolved much heat gave, under what appeared to be identical conditions, either tellurium tetrafluoride (Found: Te, 61·1; F, 36·3. Calc. for TeF_4: Te, 62·7; F, 37·3%) or a yellow liquid which could be separated into two fractions, b. p. 85—86° and 121—122°, the

former being the main constituent. The reaction with tellurium is being further examined with a view to define the conditions leading to the two types of product and to establish the nature of the compounds present in the liquid product.

The behaviour of sulphur and carbon, both of which are attacked by nitryl fluoride, was so obviously complex as to call for a more detailed study which we reserve for the future.

Element	Temperature conditions to initiate reaction	Observation	Products of reaction
H_2	200—300°	Explodes	—
Li	200—300	Burns with red flame	LiF
Na	Room temp.	Burns with yellowish-white flame	NaF, Na_2O_2 (traces of $NaNO_3$, $NaNO_2$)
K	Room temp.	Burns with lilac flame	KF, KO_2
Cu	Up to 300°	No obvious reaction	Some Cu_2O, CuO
Ag	Mild warming	First turns black then yellow	Ag_2O first formed; further heating gives AgF
Au	Up to 300°	No reaction	—
Be	Up to 300°	No reaction	—
Mg	Up to 300°	No reaction	—
Ca	Up to 300°	No reaction	—
Zn	Mild warming	Glows red and burns with yellow flame	ZnF_2, ZnO
Cd	Mild warming	Glows red	CdF_2, CdO
Hg	Mild warming	—	Hg_2F_2
B	Room temp.	Glows red	$(NO_2)BF_4$
Al	Mild warming	Glows white	AlF_3, Al_2O_3
Ti	Mild warming	Glows white	TiF_4, TiO_2
Zr	Room temp.	Glows white	ZrF_4, ZrO_2
Th	Room temp.	Glows white	ThF_4, ThO_2
Si	Room temp.	Glows red	$(NO_2)_2SiF_6$
Ge	Mild warming	No obvious heating	$(NO_2)_2GeF_6$
Sn	Mild warming	Metal melts	SnF_4, SnO_2
Pb	Mild warming	Meltal melts	PbF_2, PbO
V	Mild warming	Glows red	$(NO_2)VOF_4$,$(NO_2)VF_6$
P (red)	Room temp.	Glows red	$(NO_2)PF_6$, trace P_2O_5
As	Room temp.	—	$(NO_2)AsF_6$ trace As_2O_5
Sb	Mild warming	Becomes very hot, first forms drops of SbF_5	$(NO_2)SbF_6$ trace Sb_2O_5
Bi	200—300°	White solid forms	BiF_5 (probably)
Cr	Mild warming	—	CrO_2F_2, trace CrF_3
Mo	Room temp.	Glows white	MoO_2F_2, $MoOF_4$
W	Mild warming	Glows red	WOF_4
U	Room temp.	(*a*) Glows white, then (*b*) glows red	(*a*) UF_4, U_3O_8, UO_2; (*b*) UO_2F_2
Se	Room temp.	First forms drops of SeF_4	$(NO_2)SeF_5$
Te	Room temp.	Much heat evolved	(i) TeF_4; (ii) yellow liquids
Mn	200—300°	Glows red	MnF_2, and probably Mn_2O_3
Br	Room temp.	No reaction	—
I	Mild warming	First forms drops of IF_5	$(NO_2)IF_6$
Fe	Mild warming	Glows red	FeF_3, Fe_2O_3
Co	Mild warming	Glows red	CoF_2
Ni	Mild warming	Glows red	NiF_2, NiO

Reactions of Nitryl Fluoride with Non-Metallic Fluorides.—(i) Boron trifluoride, prepared by heating calcium fluoride with boron trioxide in concentrated sulphuric acid, was mixed with gaseous nitryl fluoride. The exothermic reaction produced white, solid nitronium tetrafluoroborate. It was analysed by dissolving it in cold aqueous sodium hydroxide and estimating the nitrogen as ammonia after reduction with Devarda's alloy. The products of hydrolysis, nitric and fluoroboric acids, were determined as the mixed nitron salt [Found: N, 9·9. Calc. for $(NO_2)BF_4$: N, 10·5%. Found, for nitron salt: C, 61·9; H, 4·86; N, 16·45. Calc. for $C_{20}H_{16}N_4HNO_3 + C_{20}H_{16}N_4HBF_4$: C, 61·9; H, 4·4; N, 16·2%].

(ii) Prepared from its elements, silicon tetrafluoride combined strongly exothermally with nitryl fluoride to give white, solid dinitronium hexafluorosilicate. Nitrogen was determined as above, and fluorine as lead chlorofluoride. Silicon was obtained by fusion with sodium carbonate–potassium nitrate, dissolving the melt in water, evaporating to dryness with hydrochloric acid, and weighing as SiO_2 [Found: Si, 11·6; F, 47·7; N, 11·8. Calc. for $(NO_2)_2SiF_6$: Si, 12·0; F, 48·7; N, 12·0%].

(iii) Germanium tetrafluoride, obtained by heating barium fluorogermanate to 700° in a silica bulb, combined in the gaseous phase with nitryl fluoride with evolution of heat to give a white solid, *dinitronium hexafluorogermanate*. Germanium was determined as the dioxide, and fluorine

as lead chlorofluoride, after the original solid had been decomposed with aqueous sodium hydroxide solution [Found : Ge, 25·5; F, 41·4; N, 10·4. $(NO_2)_2GeF_6$ requires Ge, 26·1; F, 40·9; N, 10·1%].

(iv) Phosphorus pentafluoride and nitryl fluoride gave, with slight evolution of heat, white nitronium hexafluorophosphate. Phosphorus was determined in the aqueous extract of a sodium carbonate–potassium nitrate fusion as ammonium phosphomolybdate [Found : P, 16·0; N, 7·6. Calc. for $(NO_2)PF_6$: P, 16·2; N, 7·3%].

(v) Arsenic pentafluoride, resulting from the fluorination of arsenious oxide, reacted with nitryl fluoride with slight evolution of heat to give white, solid nitronium hexafluoroarsenate. Arsenic was determined as silver arsenate from the aqueous extract of a sodium carbonate–potassium nitrate fusion [Found : As, 31·4; N, 6·3. Calc. for $(NO_2)AsF_6$: As, 31·9; N, 6·0%].

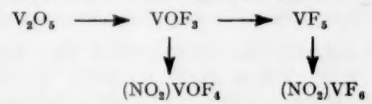
(vi) Antimony pentafluoride, from the action of fluorine on the trioxide, reacted extremely vigorously with nitryl fluoride (the pentafluoride was caused to boil) to produce white, solid nitronium hexafluoroantimonate. Passage of nitryl fluoride over the solid was continued until all the pentafluoride was consumed, after which the reaction vessel was heated at 100° under vacuum for some time. Antimony was determined as the sulphide and fluorine as calcium fluoride [Found : Sb, 43·8; F, 41·0; N, 4·6. Calc. for $(NO_2)SbF_6$: Sb, 43·2; F, 40·4; N, 5·0%].

(vii) Selenium tetrafluoride, obtained by interaction of the elements at 0°, was treated with nitryl fluoride. It became viscous and, in time, gave white, solid *nitronium pentafluoroselenite*. The compound was heated at 100° under vacuum to remove residual selenium tetrafluoride. Selenium was determined by reduction to the element with sulphur dioxide, and fluorine as lead chlorofluoride after distillation from 50% sulphuric acid [Found : Se, 36·5; F, 43·9; N, 6·4. $(NO_2)SeF_5$ requires Se, 35·9; F, 43·2; N, 6·4%].

(viii) Bromine trifluoride, prepared from its elements, was treated with a stream of nitryl fluoride. The liquid became yellow, then viscous, and appeared to have some solid in suspension. Attempts to separate this solid or to increase its amount by cooling the liquid were unavailing, as was also evaporation in a vacuum which gave a white solid containing bromine, fluorine, nitrogen, and silicon, but of indefinite composition.

(ix) Iodine pentafluoride, prepared from the elements, and saturated with nitryl fluoride, first became yellow and then yielded white, solid *nitronium hexafluoroiodate*. This was stable at low temperatures but at room temperature showed appreciable dissociation into nitryl fluoride and iodine pentafluoride. Iodine was determined by reduction with sulphur dioxide and precipitation as silver iodide, and fluorine as calcium fluoride [Found : I, 45·2; F, 40·2; N, 4·6. $(NO_2)IF_6$ requires I, 44·3; F, 39·7; N, 4·9%]. The discrepancy in the analyses corresponds to, and is probably due to, the presence of iodine pentafluoride arising from decomposition, to the extent of 7% molar.

Reactions of Nitryl Fluoride with Oxides.—(i) Vanadium pentoxide, slightly warmed in nitryl fluoride, first became a darker red, then yellow, and finally white; this material melted and rapidly reacted with more nitryl fluoride to give a vapour which froze to a white solid further along the tube. By stopping the reaction at intermediate stages, it was shown that the primary products were vanadium oxyfluoride and pentafluoride. These individually reacted with the molecule of nityl fluoride to give a mixture of the new *nitronium tetrafluoro-oxyvanadate*(v) and *nitronium hexafluorovanadate*(v) as the composite sublimate [Found : V, 25·0; F, 43·9; N, 6·8. $(NO_2)VOF_4$ requires V, 27·0; F, 40·2; N, 7·4. $(NO_2)VF_6$ requires V, 24·2; F, 54·0; N, 6·6%) :



These findings agree with those of Sharpe (*J.*, 1951, 798) who says in reference to his use of nitrogen peroxide and bromine trifluoride : " Attempts to obtain . . . nitronium hexafluorovanadates gave products intermediate in composition between the tetrafluoro-oxyvanadates and hexafluorovanadates."

(ii) Sulphur trioxide, strictly anhydrous, reacted exothermally with nitryl fluoride, first melting, then becoming yellow—owing possibly to its dissolving the nitronium ion—and finally colourless. The white solid left on cooling after the reaction was nitronium fluorosulphonate [Found : S, 23·0; F, 13·7; N, 9·6. Calc. for $(NO_2)SO_3F$: S, 22·1; F, 13·1; N, 9·7%], which had been prepared by treating sulphur trioxide with nitrogen peroxide and bromine trifluoride (Woolf, *J.*, 1950, 1053).

(iii) Selenium dioxide reacted with nitryl fluoride at room temperature to give, first, selenium tetrafluoride which then combined with more nitryl fluoride to give white, crystalline *nitronium pentafluoroselenite* [Found: Se, 36·7. $(NO)_2SeF_5$ requires Se, 35·9%].

(iv) The reaction between tellurium dioxide and nitryl fluoride proceeded steadily after being started by slight initial warming. The considerable evolution of heat kept the product, *nitronium pentafluorotellurite*, molten (m. p. ~110°). It set to a white solid on cooling [Found: Te, 47·8; F, 36·0; N, 4·9. $(NO_2)TeF_5$ requires Te, 47·5; F, 35·4; N, 5·2%]. It is noteworthy that nitryl fluoride had no action on tellurium trioxide.

(v) Nitryl fluoride had little effect on glass at room temperature, but, on slight warming, attacked it appreciably. Nitrogen dioxide was evolved and a feathery white solid was deposited on the surface of the glass. This solid was insoluble in nitryl fluoride and contained nitrogen, fluorine, silicon, and boron. Silicon and nitrogen were determined, as above, and also fluorine on a sample not subjected to fusion, in an attempt to estimate the amount of $(NO_2)_2SiF_6$ present. The analyses clearly indicate a mixture of nitronium fluorosilicate and fluoroborate, the rather high fluorine content being due to hydroysis of the BF_4^- ion [Found: Si, 11·0; F, 48·7; N, 11·8. Calc. for 90% $(NO_2)_2SiF_6$ + 10% $(NO_2)BF_4$: Si, 10·8; F, 43·7 (BF_4^- ion being assumed to be undissociated): N, 11·9%].

The authors express their indebtedness to the General Chemicals Division of Imperial Chemical Industries Limited, Runcorn, for the fluorine cell used, and to the Salters' Company for a Scholarship which enabled one of them (G. H.) to take part in the work.

KING'S COLLEGE, NEWCASTLE-ON-TYNE, 1. [*Received, November 13th*, 1953.]

Reactions of Thiols and Thioethers. Part I. An Analogue of the Mannich Reaction involving Thiols, Formaldehyde, and Active Methylene or Methylidyne Compounds.

By F. POPPELSDORF and S. J. HOLT.

[Reprint Order No. 4828.]

A new reaction is described in which indole, antipyrine, and 2-naphthol each give sulphur analogues (I), (II), and (III) of Mannich bases on treatment with formaldehyde and thiols. The products have been characterised by direct comparison with compounds formed from Mannich bases or their quaternary derivatives and thiols in the known manner and also by desulphurisation with Raney nickel.

The primary step in the new reaction is shown probably to be addition of formaldehyde to the thiol to form an alkyl- or aryl-thiomethanol.

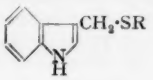
Interaction of 1-dimethylaminomethyl-2-naphthol and excess of toluene-ω-thiol at the boiling point results in a good yield of 1-methyl-2-naphthol, the thiol probably acting as a reducing agent.

Pyrolysis of 1-benzylthiomethyl-2-naphthol gives a 44% yield of 1-methyl-2-naphthol, and α-benzylthiomethyldeoxyanisoin (V) decomposes on distillation into toluene-ω-thiol and α-methylenedeoxyanisoin (VI).

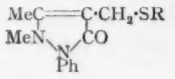
ALTHOUGH the Mannich reaction (Blicke, "Organic Reactions," John Wiley & Sons, Inc., New York, 1942, Vol. I, p. 303 *et seq.*; Mannich, U.S.P. 1,824,676) has been fairly extensively investigated, there appears to be only one recorded example in which an analogous reaction involving thiols in place of amines (Sebrell, U.S.P. 2,150,463) has been attempted. This describes the condensation of a mercaptobenzothiazole, formaldehyde, and a phenol in the presence of a catalyst such as sodium hydroxide. Resinous products of unknown composition were obtained.

The reaction $R^1R^2R^3CH + CH_2O + R^4SH \longrightarrow R^1R^2R^3C{\cdot}CH_2{\cdot}SR^4 + H_2O$, where $R^1R^2R^3CH$ represents a compound containing an active methylene or methylidyne group and R^4 is an alkyl or aryl radical, has now been found to proceed smoothly and satisfactorily with indole, antipyrine, and 2-naphthol under conditions very similar to those necessary for optimum yields of the analogous Mannich bases. The weak bases

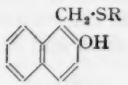
indole and antipyrine, for example, undergo the new reaction in acid medium while the weakly acidic 2-naphthol reacts only under basic conditions, the products formed being the sulphides, (I), (II), and (III).



(I)



(II)



(III)

Unlike the analogous Mannich bases, these compounds do not possess a basic group and thus proved more difficult to isolate. Several unsucessful attempts were made to isolate the sulphides *via* their mercuric chloride complexes.

Indole, aqueous 40% formaldehyde, and ethane-, propane-, *n*-butane-, or toluene-ω-thiol condensed in acetic acid at room temperature during 6 days. Vacuum-distillation of the products gave the desired sulphides (I; R = Et, Pr^n, Bu^n) in yields of about 25%. The benzyl compound (I; R = CH_2Ph), however, was formed in only 14% yield whilst in the case of thiophenol no similar product could be isolated. The low yields may be attributed to decomposition during distillation and to the formation of by-products during the reaction. Attempts to improve the yields by omission of acetic acid, or by its replacement by triethylamine, inhibited the reaction completely.

Paraformaldehyde, antipyrine, and each of the above-mentioned thiols, except ethanethiol, condensed in aqueous acetic acid at 100° in 23—47 hr. The products (II; R = Ph or CH_2Ph) were obtained in yields of about 80%, and the *n*-propyl and *n*-butyl compounds were formed in yields of 42% and 62% respectively. Ethanethiol, probably because of its low boiling point, did not react satisfactorily under the above conditions. The desired sulphide (II; R = Et) was obtained in 17% yield, however, from a mixture of ethanethiol, aqueous 40% formaldehyde, and antipyrine in aqueous acetic acid which had been allowed to stand for 14 days at room temperature. Here, too, reaction failed in a medium made alkaline with triethylamine.

2-Naphthol, aqueous 40% formaldehyde, and each of the thiols in alcoholic solution failed to react at room temperature during 6 days. However, addition of triethylamine caused exothermic reaction and after six days at room temperature the desired sulphides (II; R = Et, Pr^n, Bu^n, Ph, and CH_2Ph) were obtained in 76—89% yields. Only about half these yields were obtained after 3 days' reaction under the same conditions.

It would seem reasonable that the new reaction takes a course analogous to that of the Mannich reaction and, although the mechanism of the latter remains in some doubt, it appears likely (Bodendorf and Koralewski, *Arch. Pharm.*, 1933, **271**, 101; Lieberman and Wagner, *J. Org. Chem.*, 1949, **14**, 1001; Alexander and Underhill, *J. Amer. Chem. Soc.*, 1949, **71**, 4014) that the primary step in the reaction with secondary amines is the union with formaldehyde to give an amino-methanol: $R^1R^2NH + CH_2O \longrightarrow R^1R^2N{\cdot}CH_2{\cdot}OH$. This may then give rise to the carbonium ion $R^1R^2\overset{+}{N}{\cdot}CH_2$, which subsequently attacks the active methylidyne or methylene group (Lieberman and Wagner, *loc. cit.*). Similarly, the first step in the new reaction is probably addition of formaldehyde to the thiol to give a substituted thio-methanol: $RSH + CH_2O \longrightarrow RS{\cdot}CH_2{\cdot}OH$. Support would be provided if the alkyl- or aryl-thiomethanol gave the desired sulphide (I), (III), or (III) in similar yield when used in the reaction in place of the thiol and formaldehyde. This has been confirmed for phenylthiomethanol and antipyrine (78% yield), and for ethylthiomethanol and 2-naphthol (82% yield).

An alternative mechanism involving union of formaldehyde with the active methylidyne or methylene group: $R^1R^2R^3CH + CH_2O \longrightarrow R^1R^2R^3C{\cdot}CH_2{\cdot}OH$, although less likely, cannot be excluded as the primary process. It is improbable, however, for antipyrine, as its 4-hydroxymethyl derivative is unlikely to be produced under the acidic conditions employed (Duquénois and Métais, *Bull. Soc. chim.*, 1949, 415).

In order to confirm the structures and to compare the relative yields, some of the sulphides were prepared by treating the methiodides of the corresponding Mannich bases with a thiol in methanolic sodium methoxide solution (cf. Atkinson, Poppelsdorf, and

Williams, *J.*, 1953, 580) or by heating the Mannich base with a thiol when the quaternised Mannich base was not easily accessible (cf. Gill, James, Lions, and Potts, *J. Amer. Chem. Soc.*, 1952, **74**, 4923). In this connection, tetramethylammonium iodide was obtained in considerable amount in an attempt to quaternise 1-dimethylaminomethyl-2-naphthol with methyl iodide in chloroform (cf. the interaction of methyl iodide or methyl sulphate with gramine; Geissman and Armen, *ibid.*, p. 3916; Schöpf and Thesing, *Angew. Chem.*, 1951, **63**, 377).

In an attempt to prepare 1-benzylthiomethyl-2-naphthol (III; R = CH_2Ph) by heating 1-dimethylaminomethyl-2-naphthol with three mols. of toluene-ω-thiol under reflux until evolution of dimethylamine had ceased (5½ hr.), distillation of the resultant mixture gave a 92% yield of 1-methyl-2-naphthol. This compound was probably produced by the reduction of the Mannich base by the toluene-ω-thiol (cf. Cornforth, Cornforth, and Robinson, *J.*, 1942, 682). In this event, the simultaneous formation of dibenzyl disulphide by oxidation of the thiol might be expected. When the reaction was carried out in an atmosphere of nitrogen, to avoid the possibility of aerial oxidation of the thiol at the elevated temperature, stilbene, hydrogen sulphide, and sulphur were formed in addition to 1-methyl-2-naphthol. Thus, the intermediate formation of dibenzyl disulphide might be inferred since this compound readily decomposes to stilbene when heated, as observed by Fromm and Achert (*Ber.*, 1903, **36**, 539). The course of the reaction may be more complex because of the possibility of the intermediate formation of the benzyl sulphide (III; R = CH_2Ph). This compound (prepared by the new reaction) did in fact decompose during 5½ hr. at 210—215°, giving a 44% yield of 1-methyl-2-naphthol. Formation of the methylnaphthol in this instance may be explained by an oxidation–reduction process whereby one molecule of the sulphide is reduced at the expense of another.

It was subsequently found that 1-benzylthiomethyl-2-naphthol could, in fact, be made from equimolecular amounts of 1-dimethylaminomethyl-2-naphthol and toluene-ω-thiol at 150°.

The structures of representative compounds of types (I), (II), and (III) were also confirmed by desulphurisation by Raney nickel to the corresponding methyl compounds (Mozingo, Wolf, Harris, and Folkers, *J. Amer. Chem. Soc.*, 1943, **65**, 1013).

In ancillary experiments, α-benzylthiomethyldeoxyanisoin (V), formed in 85% yield from α-dimethylaminomethyldeoxyanisoin methiodide (IV) and sodium benzyl sulphide, decomposed on distillation into toluene-ω-thiol and α-methylenedeoxyanisoin (VI). Heating (VI) with piperidine gave a base, the hydrochloride of which proved identical with the Mannich base hydrochloride obtained from deoxyanisoin, paraformaldehyde, and piperidine hydrochloride. The structure (VI) was therefore confirmed.

(IV) $Ar{\cdot}CH(CH_2{\cdot}\overset{+}{N}Me_3\}I^-){\cdot}CO{\cdot}Ar$ $\qquad$ $Ar{\cdot}CH(CH_2{\cdot}S{\cdot}CH_2Ph){\cdot}CO{\cdot}Ar$ (V)

(VI) $Ar{\cdot}C(:CH_2){\cdot}CO{\cdot}Ar$ $\qquad$ (Ar = p-$MeO{\cdot}C_6H_4$)

The behaviour of (V) on heating recalls that of some Mannich base hydrochlorides (cf., *inter alia*, Mannich and Heilner, *Ber.*, 1922, **55**, 356; Mannich and Lammering, *ibid.*, p. 3510).

The new sulphides form colourless, almost odourless, crystalline solids. The melting points decrease from ethyl to the higher homologues, and that of the phenyl is higher than that of the benzyl compound.

The chemical properties of these sulphides will be described in a later communication.

Experimental

Light petroleum refers to the fraction of b. p. 40—60°.

Preparation of 3-*Alkyl- and* 3-*Aryl-thiomethylindoles* (I).—(*a*) Gramine (17·4 g., 0·1 mole) was added to a cooled solution of sodium (2·8 g., 0·12 g.-atom) and the thiol (0·12 mole) in anhydrous methanol (200 ml.). Methyl sulphate (12·6 g., 0·1 mole) was then cautiously added in two portions. After the exothermic reaction had abated, the mixture was heated under reflux whilst protected from atmospheric moisture until evolution of trimethylamine had ceased (*ca.* 20 hr.), then poured into water and extracted with ether (2 × 100 ml.). The combined

extracts were washed in succession with water, 10% hydrochloric acid (to remove unchanged gramine), water, saturated sodium hydrogen carbonate solution, and with water. The dried ($MgSO_4$) ethereal solution was evaporated to dryness, yielding the crude sulphide.

(*b*) Aqueous 40% formaldehyde (8·2 ml., 0·11 mole) was added to indole (11·7 g., 0·1 mole), the thiol (0·12 mole), and acetic acid (15 ml.). A slight exothermic reaction ensued after a short while and a clear, homogeneous solution resulted. This was kept at room temperature for 6 days and then shaken with ether (100 ml.). The ethereal solution was washed with water (2 × 50 ml.), saturated aqueous sodium hydrogen carbonate until free from acid, and finally with water (50 ml.). After drying ($MgSO_4$) and evaporation of the solvent, a syrup was obtained which yielded the sulphide on vacuum-fractionation.

(*c*) Gramine (1·74 g., 0·01 mole) and the thiol (0·01 mole) were heated together in an oil-bath at 150—160° until evolution of dimethylamine was complete (*ca.* 45 min.). The product usually crystallised and gave the pure sulphide on recrystallisation.

The *sulphides* are recorded in Table 1; they formed colourless leaflets. When produced by the different methods they had identical m. p.s and unchanged mixed m. p.s.

4-*Dimethylaminomethylantipyrine Methiodide.*—Glacial acetic acid (75 ml.) was added to cooled aqueous 33% (w/v) dimethylamine (75 ml., 0·5 mole), and the solution added to antipyrine (94·0 g., 0·5 mole). The mixture was then treated with aqueous 40% formaldehyde (41·0 ml., 0·55 mole), an exothermic reaction setting in after stirring for a short while, giving a

TABLE 1. 3-*Alkyl- and* 3-*aryl-thiomethylindoles* (I).

Comparison of yields (%).

Method of prep.	R =	Et	Pr^n	Bu^n	Ph	$Ph\cdot CH_2$
(*a*)		63 [a]	74 [a]	67 [a]	—	—
(*b*)		24	26	23	—	14
(*c*)		—	—	—	78	87

[a] These yields take recovered gramine into account.

	R	Crystd. from	M. p.	Found (%) C	H	N	S	Formula	Required (%) C	H	N	S
Et	.....	Pet [f]	51·5° [b]	69·2	6·7	7·3	16·6	$C_{11}H_{13}NS$	69·0	6·8	7·3	16·8
Pr^n	.....	Pet	46·5 [c]	70·4	7·5	6·8	15·8	$C_{12}H_{15}NS$	70·2	7·4	6·8	15·6
Bu^n	.....	Pet	42·5 [d]	71·4	7·9	6·4	15·0	$C_{13}H_{17}NS$	71·2	7·8	6·4	14·6
Ph	.....	1, EtOH 2, Pet	84	74·9	5·4	6·0	13·8	$C_{15}H_{13}NS$	75·3	5·5	5·9	13·4
$Ph\cdot CH_2$ [g]	...	1, EtOH 2, Pet	74 [e]	—	—	—	—	—	—	—	—	—

[b] B. p. 180—184°/3 mm. [c] B. p. 160—166°/0·5 mm. [d] B. p. 168—172°/0·7 mm. [e] B. p. 186—190°/2 mm. [f] Light petroleum. [g] Found: N, 5·6. Calc. for $C_{16}H_{15}NS$: N, 5·5%.

homogeneous solution. The mixture was kept at room temperature for 3 days and then poured into cold water (500 ml.). The resulting solution was extracted with chloroform (3 × 100 ml.), and the aqueous layer made alkaline to phenolphthalein with 40% aqueous sodium hydroxide. The Mannich base was extracted with chloroform (3 × 150 ml.) and the dried ($MgSO_4$) extracts were evaporated to *ca.* 250 ml. and chilled. Methyl iodide (31·0 ml., 0·5 mole) was cautiously added (vigorous exothermic reaction) and the mixture heated under reflux for 30 min., then kept overnight at 0°. The *methiodide* separated as a colourless solid (154 g., 80%); after being washed with a little chloroform and ether, it had m. p. 218° (Found: C, 46·5; H, 5·9; N, 10·4; I^-, 32·9. $C_{15}H_{22}ON_2I$ requires C, 46·5; H, 5·7; N, 10·85; I^-, 32·8%).

Preparation of 4-*Alkyl- and -Aryl-thiomethylantipyrines* (II).—(*a*) The thiol (0·06 mole) and 4-dimethylaminomethylantipyrine methiodide (19·35 g., 0·05 mole) were added in turn to a cooled solution of sodium (1·4 g., 0·06 mole) in anhydrous methanol (100 ml.). The mixture was heated under reflux whilst protected from atmospheric moisture until evolution of trimethylamine ceased (48—72 hr.), and then evaporated to dryness. Extraction of the residue with hot benzene followed by concentration of the extract and slow addition of light petroleum gave the crude sulphide which crystallised.

(*b*) A mixture of antipyrine (9·4 g., 0·05 mole), the thiol (0·06 mole), paraformaldehyde (2·25 g., 0·075 mole), acetic acid (7·5 ml.), and water (5·0 ml.) was heated on the steam-bath at 100° for 23 hr. (47 hr. for propanethiol). The cooled product was dissolved in chloroform (100 ml.), and the solution washed in succession with water, saturated sodium hydrogen carbonate solution until free from acid, and again water. After being dried ($MgSO_4$) the solution was

evaporated to dryness at atmospheric pressure and the residue heated at 100°/100 mm. for 15 min. and then at 100°/0·5 mm. for 30 min. The residual oil was dissolved in dry benzene (15 ml.) and the crude sulphide precipitated by the addition of light petroleum. After chilling at 0°, the solid was collected, washed with a little light petroleum, and dried *in vacuo* at room temperature. Purification of the benzyl and phenyl compounds was accomplished by direct crystallisation at this stage, but it was necessary first to extract the crude butyl and propyl sulphides with light petroleum. The crude compounds obtained by evaporation of these extracts were then purified directly by crystallisation.

4-Ethylthiomethylantipyrine. A solution of antipyrine (18·8 g., 0·1 mole), ethanethiol (8·9 ml., 0·12 mole), and aqueous 40% formaldehyde (8·2 ml.) in acetic acid (15 ml.) and water (6 ml.) was kept at room temperature for 14 days. The product was worked up as above except that the crude oil was distilled *in vacuo* and the fraction of b. p. 184°/0·5 mm. collected.

The *sulphides* are listed in Table 2 and formed colourless prisms.

TABLE 2. *4-Alkyl- and 4-aryl-thiomethylantipyrines* (II).

Method of prepn.	R =	Comparison of yields (%).[a] Et	Pr^n	Bu^n	Ph	Ph·CH$_2$
(*a*)		85	84	84	91	84
(*b*)		17	42	62	80	83

[a] Calc., in case of method *a*, on methiodide used.

R	Crystd. from	M. p.	Found (%) C	H	N	S	Formula	Required (%) C	H	N	S
Et	H_2O	97°[c]	63·8	7·0	10·4	11·9	$C_{14}H_{18}ON_2S$	64·1	6·9	10·7	12·2
Pr^n	C_6H_6–Pet[b]	64—65	64·9	7·0	10·5	11·4	$C_{15}H_{20}ON_2S$	65·2	7·3	10·1	11·6
Bu^n	Pet	53·5—54	66·2	7·2	9·7	11·3	$C_{16}H_{22}ON_2S$	66·2	7·6	9·7	11·0
Ph	MeOH–H_2O (2 : 1)	102—103	69·4	5·8	9·0	10·3	$C_{18}H_{18}ON_2S$	69·7	5·8	9·0	10·3
Ph·CH$_2$...	MeOH–H_2O (2 : 1)	100	70·0	6·4	9·0	10·2	$C_{19}H_{20}ON_2S$	70·4	6·2	8·6	9·9

[b] Light petroleum. [c] B. p. 184°/0·5 mm.

Preparation of 1-Alkyl- and -Aryl-thiomethyl-2-naphthols (III).—Aqueous 40% formaldehyde (8·2 ml.) was added to a mixture of 2-naphthol (14·4 g., 0·1 mole), the thiol (0·11 mole), ethanol (10 ml.), and triethylamine (5·0 ml.). An exothermic reaction ensued after the mixture had been shaken for a short while, and the 2-naphthol dissolved. After being kept at room temperature for 6 days the mixture was dissolved in ether (100 ml.), washed with water (2 × 50 ml.), dried ($MgSO_4$), and evaporated to dryness at atmospheric pressure, and the residue was heated at 100°, first at 100 mm. for 15 min., then for 30 min. at 0·5 mm. The resulting oil crystallised and contained *ca.* 90% of the sulphide, which was purified by crystallisation from a suitable solvent.

The *sulphides* prepared in this way are listed in Table 3. They formed colourless prisms.

TABLE 3. *1-Alkyl- and 1-aryl-thiomethyl-2-naphthols* (III).

R	Yield (%)	Crystd. from	M. p.	Found (%) C	H	Formula	Reqd. (%) C	H
Et[a]	89	Pet	52—52·5°	71·5	6·4	$C_{13}H_{14}OS$	71·5	6·5
Pr^n	89	Pet	49·5	72·7	6·9	$C_{14}H_{16}OS$	72·4	6·9
Bu^n	87	Pet	48	73·0	7·4	$C_{15}H_{18}OS$	73·1	7·4
Ph	76	Toluene	126—127	76·9	5·2	$C_{17}H_{14}OS$	76·7	5·3
Ph·CH$_2$ ...	86	*cyclo*Hexane	89	77·1	5·7	$C_{18}H_{16}OS$	77·2	5·8

[a] Found: S, 14·3. $C_{13}H_{14}OS$ requires S, 14·7%.

1-Benzylthiomethyl-2-naphthol from 1-Dimethylaminomethyl-2-naphthol and Toluene-ω-thiol.—1-Dimethylaminomethyl-2-naphthol (2·01 g., 0·01 mole) and toluene-ω-thiol (1·24 g., 0·01 mole) were heated for 1 hr. in an oil-bath at 150°. A brown gum was obtained on cooling, which on crystallisation from benzene–light petroleum gave a light brown solid (2·27 g.), m. p. 79—80°. Repeated extraction with boiling light petroleum removed the sulphide. Evaporation of the combined extracts produced almost colourless prisms (2·04 g., 73%), m. p. and mixed m. p. 89° (Found: S, 11·8. Calc. for $C_{18}H_{16}OS$: S, 11·4%).

Interaction of 1-*Dimethylaminomethyl-2-naphthol and Excess of Toluene-ω-thiol.*—(*a*) 1-Dimethylaminomethyl-2-naphthol (10·06 g., 0·05 mole) and toluene-ω-thiol (18·6 g., 0·15 mole) were heated under reflux for 5½ hr. Evolution of dimethylamine was then complete. The product was distilled *in vacuo* and the fraction of b. p. 115—130°/0·9 mm. collected. It solidified and crystallised from benzene–light petroleum as very pale yellow needles (7·3 g., 92%), m. p. 110° (mixed m. p. with 1-methyl-2-naphthol, 110—111°).

(*b*) The same quantities of reactants were used but the mixture was heated under reflux for 2½ hr. with a stream of dry nitrogen passing through the boiling solution. Evolution of dimethylamine was rapid at first and ceased at the end of the reaction period. Some hydrogen sulphide was also evolved. The reaction product solidified on cooling and was dissolved in and ether (120 ml.). The solution was extracted with 10% aqueous sodium hydroxide (2 × 50 ml.), and the alkaline extract filtered from a small quantity of sulphur, cooled, and made acid to Congo-red with hydrochloric acid. An oil separated which, after being stirred and cooled, gave a brown solid (6·38 g.), m. p. 99—100°. This was crystallised in succession from benzene–light petroleum, *cyclo*hexane, aqueous ethanol (charcoal), and hot water, to give 1-methyl-2-naphthol, as colourless needles (5·3 g., 67%), m. p. and mixed m. p. 111°.

The ethereal solution, after being extracted with alkali, was dried ($MgSO_4$) and evaporated to dryness, producing a solid which, after crystallisation from ethanol (charcoal), was dissolved in excess ethanol. Successive crops of crude stilbene were obtained (total 2·77 g.) on stepwise evaporation of the solution. (No attempt was made to isolate more stilbene from the mother liquors.) Recrystallisation from ethanol afforded flat, colourless prisms (2·62 g.), m. p. 125°, mixed m. p. 124—125°. The ultra-violet absorption spectrum was identical with that of stilbene.

Pyrolysis of 1-*Benzylthiomethyl-2-naphthol* (III; R = Ph·CH_2).—The benzyl sulphide (10·0 g.) was heated for 5½ hr. at 210—215°. A little hydrogen sulphide was evolved. Distillation of the dark brown product *in vacuo* gave a fraction, b. p. 95—110°/0·3 mm., solidifying to a yellow solid (3·6 g.). Crystallisation from benzene–light petroleum gave almost colourless fine needles (2·5 g.), m. p. 111°. The mixed m. p. with 1-methyl-2-naphthol was 111° (Found: C, 83·9; H, 6·4. Calc. for $C_{11}H_{10}O$: C, 83·5; H, 6·4%).

Attempted Preparation of 1-*Dimethylaminomethyl-2-naphthol Methiodide.*—Methyl iodide (3·1 ml.) was added to a cooled solution of 1-dimethylaminomethyl-2-naphthol (10·06 g., 0·05 mole) in chloroform (20 ml.), causing an immediate opalescence. The mixture was heated under reflux for 1 hr., an equal volume of dry ether added to the cooled mixture, and heating under reflux continued for a further 30 min. After cooling, the supernatant liquid was decanted and the gummy residue dissolved in hot methanol. On chilling, the solution deposited colourless crystals of tetramethylammonium iodide (3·79 g.), m. p. >300°. A sample was recrystallised first from methanol, then from water (Found: N, 6·8; I^-, 62·5. Calc. for $C_4H_{12}NI$: N, 7·0; I^-, 63·1%). The filtrate gave a brown, uncrystallisable gum on evaporation to dryness.

Desulphurisation of the Sulphides (I; R = Bu^n), (II; R = Et), *and* (III; R = Et).—The method of Mozingo, Wolf, Harris, and Folkers (*J. Amer. Chem. Soc.*, **1943**, **65**, 1013) was used, 98% ethanol being the medium in which the desulphurisations were carried out. The corresponding methyl compounds were obtained: Skatole (62%), m. p. and mixed m. p. 96°, after two crystallisations from light petroleum (Found: N, 10·4. Calc. for C_9H_9N: N, 10·7%); 4-methylantipyrine (56%), m. p. 80° (from *cyclo*hexane) (Found: C, 71·4; H, 6·6. Calc. for $C_{12}H_{14}ON_2$: C, 71·3; H, 7·0%); 1-methyl-2-naphthol (75%), m. p. 110° (from benzene–light petroleum) (Found: C, 83·2; H, 6·5. Calc. for $C_{11}H_{10}O$: C, 83·5; H, 6·4%).

α-*Dimethylaminomethyldeoxyanisoin Hydrochloride.*—Deoxyanisoin (25·6 g., 0·1 mole), dimethylamine hydrochloride (9·8 g., 0·11 mole), paraformaldehyde (4·5 g., 0·15 mole), and glacial acetic acid (52 ml.) were heated under reflux for 1 hr. and then evaporated to dryness *in vacuo*. The gum thus obtained was extracted with ether (2 × 50 ml.) and dissolved in boiling ethanol (100 ml.). Crystallisation began after concentration of the solution to *ca.* 100 ml., and was completed by cooling, addition of ether (150 ml.) with stirring, and chilling at 0° for 1 hr. The solid, recrystallised from ethanol–ether, afforded the colourless *hydrochloride* (24·1 g., 69%), m. p. 172° (Found: C, 65·1; H, 6·6; N, 4·0; Cl^-, 10·4. $C_{19}H_{24}O_3NCl$ requires C, 65·3; H, 6·6; N, 4·0; Cl^-, 10·2%). The free *base* was obtained by the action of alkali on the hydrochloride and separated as an oil which, on cooling and trituration with light petroleum, gave a colourless crystalline solid, m. p. 61° (Found: C, 72·7; H, 7·1; N, 4·5. $C_{19}H_{23}O_3N$ requires C, 72·8; H, 7·35; N, 4·5%).

The *methiodide* (IV) of the base was prepared in chloroform and crystallised from methanol as a colourless solid (76%), m. p. 190° (decomp.) (Found: C, 52·5; H, 5·7; N, 3·0; I^-, 28·0. $C_{20}H_{26}O_3NI$ requires C, 52·8; H, 5·7; N, 3·1; I^-, 27·9%).

α-*Benzylthiomethyldeoxyanisoin* (V).—α-Dimethylaminomethyldeoxyanisoin methiodide (13·65 g., 0·03 mole) was added to a solution of sodium benzyl sulphide (0·033 mole) in anhydrous methanol (100 ml.). The mixture was heated under reflux until the evolution of trimethylamine was complete (84 hr.) and then evaporated to dryness, first at atmospheric pressure, then *in vacuo*. Hot benzene extraction of the semi-solid residue, followed by evaporation to dryness of the extract *in vacuo*, gave a viscous yellow oil (11·65 g.) which crystallised during several weeks at room temperature. Crystallisation of the solid from ethanol gave colourless prisms of the *benzyl sulphide* (10·0 g. 85%), m. p. 83·5°. Two further recrystallisations from ethanol raised the m. p. to 87° (Found: C, 73·2; H, 6·0; S, 8·4. $C_{24}H_{24}O_3S$ requires C, 73·4; H, 6·2; S, 8·2%).

Decomposition of α-Benzylthiomethyldeoxyanisoin.—The benzyl sulphide (8·0 g.) decomposed on attempted distillation *in vacuo*. The fraction (3·4 g.), b. p. 182—184°/0·2 mm., formed an almost colourless oil which crystallised. Crystallisation from ethanol gave *α-methylenedeoxyanisoin* (VI) as colourless prisms, m. p. 58° (Found: C, 76·0; H, 5·8. $C_{17}H_{16}O_3$ requires C, 76·1; H, 6·0%).

α-*Piperidinomethyldeoxyanisoin Hydrochloride.*—(*a*) Prepared in a similar way to the Mannich dimethylamino-base hydrochloride, this *salt* was obtained as colourless prisms (56%), m. p. 184° after crystallisation from ethanol–ether (Found: C, 67·8; H, 7·25; N, 3·9; Cl^-, 9·0. $C_{22}H_{28}O_3NCl$ requires C, 67·8; H, 7·24; N, 3·6; Cl^-, 9·1%).

(*b*) α-Methylenedeoxyanisoin (2·00 g., 0·0075 mole) and piperidine (4·0 ml., 0·041 mole) were heated at 100° for 14 hr. Excess of piperidine was then removed *in vacuo* and the cooled residual orange oil washed by decantation with water (2 × 10 ml.). The oil was dissolved in benzene (30 ml.) and washed with water (15 ml.). After being dried ($MgSO_4$), the benzene solution was saturated with dry gaseous hydrogen chloride and evaporated to half its bulk at atmospheric pressure. Cooling and scratching afforded pale buff crystals of α-piperidinomethyldeoxyanisoin hydrochloride (2·90 g.), m. p. 180—183°. Crystallisation from ethanol–ether gave very small, almost colourless prisms (2·20 g., 76%), m. p. 183—184°, mixed m. p. 184° (Found: N, 3·9%).

Interaction of Ethylthiomethanol and Antipyrine.—Triethylamine (2·5 ml.) was added to a mixture of 2-naphthol (7·2 g., 0·05 mole), ethylthiomethanol (Levi, *Gazzetta*, 1932, **62**, 775) (5·1 g., 0·055 mole), ethanol (5 ml.), and water (5 ml.). A very slight exothermic reaction ensued, all the 2-naphthol dissolved, and the mixture separated into two layers. After being kept at room temperature for 6 days with occasional shaking, the mixture was worked up as before, to give pale yellow prisms of 1-ethylthiomethyl-2-naphthol (8·9 g., 82%), m. p. and mixed m. p. 52°.

Interaction of Phenylthiomethanol and Antipyrine.—A mixture of antipyrine (9·4 g., 0·05 mole), phenylthiomethanol (Levi, *loc. cit.*) (7·7 g., 0·055 mole), acetic acid (7·5 ml.), and water (5·0 ml.) was heated at 100° for 23 hr. Working up afforded colourless rectangular prisms of 4-phenylthiomethylantipyrine (12·05 g., 78%), m. p. and mixed m. p. 102—103°.

One of the authors (F. P.) thanks the Directors of the British Drug Houses Ltd. for permission to publish this paper and for the generous provision of laboratory facilities.

The British Drug Houses Ltd.,
London, N.1.
The Courtauld Institute of Biochemistry,
Middlesex Hospital Medical School, London, W.1. [*Received, November 24th,* 1953.]

*The Oxidation of Phenylhydrazones. Part II.**

By B. M. Lynch and K. H. Pausacker

[Reprint Order No. 4830.]

The rates of oxidation of various nuclear-substituted benzaldehyde phenylhydrazones with perbenzoic acid have been determined at three temperatures, and the entropies, free energies, and heats of activation have been calculated. A theory is advanced for the mechanism of the reaction.

It has been shown that benzylazoxybenzenes are formed in excellent yields by the oxidation of nuclear-substituted benzaldehyde phenylhydrazones with perbenzoic and perphthalic acid (Part I *; Witkop and Kissman, *J. Amer. Chem. Soc.*, 1953, **75**, 1975):

$$Ar{\cdot}CH{:}N{\cdot}NHAr' + Ph{\cdot}CO_3H \longrightarrow Ar{\cdot}CH_2{\cdot}N(O){:}NAr' + Ph{\cdot}CO_2H$$

In this paper, the rates of the reaction of perbenzoic acid with substituted benzaldehyde phenylhydrazones have been measured by determining the "active" oxygen remaining after different times.

The solvent was diethyl ether, and measurements were made at three temperatures; only freshly prepared solutions of perbenzoic acid were used, since it was found that the rate increased when samples of perbenzoic acid which had undergone some spontaneous decomposition were used (cf. Friess, *J. Amer. Chem. Soc.*, 1949, **71**, 2571; Doering and Speers, *ibid.*, 1950, **72**, 5515; Badger, Buttery, and Lewis, *J.*, 1953, 2143).

The rates of the reactions studied were unaffected by exposure to daylight, unlike the similar oxidations of aromatic azo-compounds with perbenzoic acid (Badger *et al.*, *loc. cit.*).

Experimental

M.p.s are corrected.

Reagents.—Perbenzoic acid was prepared by Braun's method (*Org. Synth.*, Coll. Vol. I., 1946, p. 431) except that diethyl ether was used to extract the peracid. The minimum purity, estimated by iodometric titration, was 92·0%.

Diethyl ether was purified by Vogel's method ("A Textbook of Practical Organic Chemistry," Longmans, 1950, p. 162).

Benzene was purified by Vogel's method (*op. cit.*, p. 171) and dried over sodium.

Substituted benzaldehyde phenylhydrazones were prepared by condensation of the appropriate benzaldehyde and phenylhydrazine in ethanol, and were crystallised from aqueous ethanol immediately before use. Their m. p.s are given in the following Table. M. p.s in parentheses are those reported in the literature. In benzaldehyde phenylhydrazone the positions in the Ph·NH group are indicated by primed numerals.

No.	1	2	3	4	5	6	7	8
Substituent	3-OMe	4-OMe	3′-OMe	4′-OMe	3-Me	4-Me	3′-Me	4′-Me
M. p.	76° (76°)	122° (120°)	101° (101°)	124° (123°)	88° (87°)	112° (112°)	100° (96°)	126° (125°)
No.	9	10	11	12	13	14	15	16
Substituent	Nil	3-Cl	4-Cl	3′-Cl	4′-Cl	3-NO_2	4-NO_2	3′-NO_2
M. p.	158° (157°)	136° (134°)	129° (127°)	133° (133°)	129° (127°)	122° (120°)	158° (155°)	131° (131°)

Apparatus.—A bath was used whose temperature was controlled within ± 0·05°. Reactions were performed in calibrated standard 50-ml. or (with sparingly soluble phenylhydrazones) 100-ml. flasks.

Method of Estimation.—The phenylhydrazone (*ca.* 3—5 × 10^{-3} mole) was weighed into the reaction vessel, which was placed in the bath until temperature equilibrium was attained. A pre-heated solution of perbenzoic acid (*ca.* 8—10 × 10^{-2}M) was added to the mark, and the mixture was vigorously shaken. When the phenylhydrazone dissolved slowly, it was first dissolved in diethyl ether in the flask and then a known volume of a solution of perbenzoic acid was added, together with diethyl ether to make up to the mark. Aliquots (2 ml.) were withdrawn at determined times and added to a mixture of carbon tetrachloride (10 ml.), 0·2N-

* Part I, *J.*, 1953, 2517.

potassium iodide (5 ml.), and 2N-sulphuric acid (5 ml.). The liberated iodine was titrated with 0·04N-sodium thiosulphate (starch). Attempted estimation in the absence of carbon tetrachloride gave unsatisfactory end-points. The perbenzoic acid solution was also estimated immediately before use.

Results.—Reactions were followed to at least 50% completion, and were found to follow pure second-order kinetics. The rate constants were calculated by standard methods and were found to obey the Arrhenius equation.

The reaction of *m*-nitrobenzaldehyde phenylhydrazone with perbenzoic acid at 25° is given as a typical example in Table I.

TABLE 1.

Initial phenylhydrazone concn. = 0·07430M (8·08 ml. of 0·03764N-$Na_2S_2O_3$).
Initial perbenzoic acid concn. = 0·0864M (9·39 ml. of 0·03764N-$Na_2S_2O_3$).
First perbenzoic acid estimation = 9·10 ml.
Equivalent phenylhydrazone concn. = 7·79 ml.

Time (min.)	4·8	10·8	18·0	23·3	33·3	40·0	44·3	53·0	77·0	110·0
Titre (ml.)	8·86	8·60	8·28	8·10	7·74	7·53	7·35	7·10	6·67	5·74
10^3k_2 (mole^{-1} l. sec.$^{-1}$)	1·299	1·250	1·257	1·239	1·240	1·238	1·210	1·261	1·252	1·250

Mean : $k_2 = 1{\cdot}25 \times 10^{-3}$ mole^{-1} l. sec.$^{-1}$.

Results obtained at different temperatures are (averages in parentheses) :

Temp.	15·00°	20·30°	25·00°
10^3k_2 (mole^{-1} l. sec.$^{-1}$)	0·661, 0·675 (0·668)	0·920, 1·00 (0·960)	1·25, 1·25 (1·25)

The bimolecular constants obey the Arrhenius equation, as shown by the following data (the calculated values are given by $k = 5{\cdot}72 \times 10^4\, e^{-10,450/\boldsymbol{R}T}$) :

Temp.	15·00°	20·30°	25·00°
10^3k_2 obs.	0·668	0·960	1·25
10^3k_2 calc.	0·664	0·947	1·257

The results obtained with the various benzaldehyde phenylhydrazones are summarised in Table 2, duplicates being shown :

TABLE 2. *Perbenzoic acid oxidation of substituted benzaldehyde phenylhydrazones.**

(a) *Reactions in diethyl ether.*

No.	10^3k † 15°	20°	25°	$\log_{10}A$	$\Delta H^\ddagger$	$\Delta F^\ddagger$	$-\Delta S^\ddagger$	X	Y	Z
1	6·16, 6·16, 6·28	8·06, 7·87	10·0, 10·1	4·02	7·6	20·2	43·1	−0·2	0·2	−0·4
2	23·1, 23·6	28·9, 30·9	33·8, 36·1	3·80	6·6	19·4	43·7	−1·2	−0·1	−1·1
3	3·38, 3·42	9·25, 9·54	11·79, 12·00	4·02	7·5	20·1	43·1	−0·3	0·2	−0·5
4	40·4, 40·5	49·8, 49·6	60·4, 60·8	3·84	6·3	19·1	43·7	−1·5	−0·2	−1·3
5	3·90, 3·85	4·90, 5·08	6·30, 6·41	3·96	7·8	$20{\cdot}4_5$	43·7	0·0	0·15	−0·15
6	6·01, 6·05	7·60, 7·74	9·74, 9·80	4·91	7·6	20·2	43·1	−0·2	0·2	−0·4
7	4·28, 4·22	5·52, 5·55	7·04, 7·00	4·00	7·8	20·4	43·1	0·0	0·2	−0·2
8	6·99, 6·81	8·70, 8·80	11·2, 11·0	3·98	7·5	20·1	43·1	−0·3	0·2	−0·5
9	3·16, 3·10	3·94, 4·09	5·05, 5·20 [a]	3·87	7·8	20·6	43·7	0	0	0
10	1·43, 1·46	1·82, 1·92	2·43, 2·45	4·13	8·6	21·0	42·9	0·8	0·4	0·4
11	2·49, 2·49 [b]	3·05, 3·07 [c]	3·53, 3·61	4·06	8·3	20·8	42·9	0·5	0·3	0·2
12	0·506, 0·513	0·667, 0·683	0·896, 0·917	4·15	9·2	21·6	42·5	1·4	0·4	1·0
13	1·54, 1·55 [b]	1·72, 1·73	2·25, 2·24 [d]	4·11	8·6	21·1	42·9	0·8	0·3	0·5
14	0·661, 0·675	0·920, 1·00	1·25, 1·25	4·76	$9{\cdot}8_5$	21·4	39·6	$2{\cdot}0_5$	1·2	0·8
15	0·298, 0·318	0·431, 0·455	0·582, 0·610	5·80	11·7	21·9	35·0	3·9	2·6	1·3
16	0·295, 0·297 [b]	0·339, 0·337	0·463, 0·469	4·82	10·5	22·0	39·3	2·7	1·3	1·4

* $\Delta H_0^\ddagger$, $\Delta F_0^\ddagger$ (in kcal.), and $\Delta S_0^\ddagger$ (in cal. deg.$^{-1}$) are the heat of activation, the free energy of activation, and the entropy of activation, respectively, for the unsubstituted benzaldehyde phenylhydrazone. $X = \Delta H^\ddagger - \Delta H_0^\ddagger$; $Y = T(\Delta S^\ddagger - \Delta S_0^\ddagger)$; $Z = \Delta F^\ddagger - \Delta F_0^\ddagger$; all in kcal. $\Delta F^\ddagger$ and $\Delta S^\ddagger$ for the various compounds are calculated from the rates at 25°. A is the frequency factor.

[a] When an equimol. mixture of benzoic and perbenzoic acid was used, 10^3k was 6·26, 6·43. [b] Both values at 18°. [c] Both values at 22°. [d] At 28°, 2·66. † Mole^{-1} l. sec.$^{-1}$.

(b) *Reaction in benzene.* Only the unsubstituted benzaldehyde phenylhydrazone was investigated. The reaction was of second order and the rates of reaction followed the Arrhenius equation. Summarised results are :

Temp.	20°	25°	35°
10^3k	18·2, 19·2	23·6, 22·8	35·8, 34·8

$k = 5{\cdot}25 \times 10^8\, e^{-7,310/\boldsymbol{R}T}$ mole^{-1} l. sec.$^{-1}$.
$\Delta F^\ddagger = 19{\cdot}7$ kcal., $\Delta S^\ddagger = -44{\cdot}5$ cal. deg.$^{-1}$.

Discussion

Two mechanisms can be postulated which satisfy the observed second-order kinetics:

Mechanism (I):

$$Ph\cdot CH{:}N\cdot NHPh + Ph\cdot CO_3H \xrightarrow[(1)]{\text{Slow}} Ph\cdot CH{:}N(O)\cdot NHPh + Ph\cdot CO_2H$$

$$Ph\cdot CH{:}N(O)\cdot NHPh \xrightarrow[(2)]{\text{Fast}} Ph\cdot CH_2\cdot N(O){:}NPh$$

Mechanism (II):

$$Ph\cdot CH{:}N\cdot NHPh \underset{(1)}{\overset{\text{Fast}}{\rightleftharpoons}} Ph\cdot CH_2\cdot N{:}NPh$$

$$Ph\cdot CH_2\cdot N{:}NPh + Ph\cdot CO_3H \xrightarrow[(2)]{\text{Slow}} Ph\cdot CH_2\cdot N(O){:}NPh + Ph\cdot CO_2H$$

Step (2) of mechanism (I) is analogous to the reversion of an *aci*-nitro-compound to the stable isomer. The intermediate of mechanism (II) has been isolated by several workers (Thiele, *Annalen*, 1910, **376**, 267; Gallagher, *Bull. Soc. chim.*, 1921, **29**, 683; Uemura and Inamura, *Bull. Chem. Soc. Japan*, 1935, **10**, 169) but no quantitative studies of its equilibrium with benzaldehyde phenylhydrazone have been made. The slow step (2) of mechanism (II) involves the oxidation of an azo-compound to the corresponding azoxy-compound by perbenzoic acid, which is known to occur readily with both aliphatic and aromatic azo-compounds (cf. Langley, Lythgoe, and Rayner, *J.*, 1952, 4191; Swern, *Chem. Reviews*, 1949, **45**, 1).

Since the entropy of activation is approximately constant for all the compounds investigated (excepting the nitro-substituted compounds), either the free energies or the heats of activation may be used to interpret the effects of substituents. Although there is not a very large change in the free energies and heats of activation, electron-donating substituents decrease these quantities, whereas electron-accepting substituents increase them. The qualitative effects of substituents are therefore in agreement with the established nature of per-acids as electrophilic reagents (Swern, *loc. cit.*; *J. Amer. Chem. Soc.*, 1947, **69**, 1692; Derbyshire and Waters, *Nature*, 1950, **165**, 401). The effect of substituents is more apparent when the rates of the various substituted compounds (10^3k at 25°) are listed: 4′-OMe (60·6) > 4-OMe (35·5) > 3′-OMe (11·9) > 4′-Me (11·1) > 3-OMe (10·1) > 4-Me (9·8) > 3′-Me (7·0) > 3-Me (6·35) > H (5·1) > 4-Cl (3·6) > 3-Cl (2·4) > 4′-Cl (2·25) > 3-NO_2 (1·25) > 3′-Cl (0·91) > 4-NO_2 (0·60) > 3′-NO_2 (0·47). The 4′-NO_2-substituted compound reacted too slowly for measurements to be made. In all cases, the effects of substituents in the Ph·NH ring are more marked than in the Ph·CH ring.

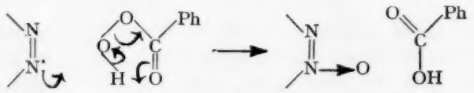
This evidence lends strong support to mechanism (II), in which the former ring is conjugated with the reactive centre, whereas in mechanism (I) this applies to the other ring. Thus the effects of substituents in the Ph·NH ring will be more marked if mechanism (II) is correct. Substituents in the other ring would, of course, exert the same type of overall effect but as it is separated from the reactive centre by a methylene group and is thus not conjugated with the point of attack the effects would be smaller.

The effects of substituents in this reaction are noticeably different from their effects on the autoxidation of benzaldehyde phenylhydrazone (Pausacker, *J.*, 1950, 3478). In the latter case it was found that all substituents in the Ph·CH ring lowered the rate of reaction, whereas the rates of compounds substituted in the Ph·NH ring obeyed Hammett's equation. This is due to the free-radical nature of the autoxidation reaction.

The low values of the frequency factor (10^4—10^6) for the per-acid oxidations lend further support to mechanism (II). It has been shown (cf. Moelwyn-Hughes, "Kinetics of Reactions in Solution," Oxford Univ. Press, 1947, p. 235) that "slow" (*i.e.*, $A < 10^{12}$—10^{13}) reactions may be caused by the fact that an added substance may exist in equilibrium with a very small proportion of another compound which is the actual reacting entity. According to mechanism (II), if the logical assumption is made that the azo-compound has a small equilibrium concentration compared with the hydrazone, then the "slow" nature of the reaction is satisfactorily explained.

With regard to the actual mode of action of perbenzoic acid, it has been assumed (Witkop and Kissman, *loc. cit.*) that attack by a hydroxyl cation is involved, by analogy with the mechanism previously proposed (cf. Swern, " Organic Reactions," Wiley, 1953, Vol. VII, p. 386) for the reaction of olefins with per-acids. Our results show that the entropy of activation of the perbenzoic acid oxidation of benzaldehyde phenylhydrazone is virtually identical in benzene and in diethyl ether. The energy of activation is actually less (and the rate is greater) in benzene solution. If the reaction is ionic this would not be expected, as the more polar diethyl ether would be expected to increase the rate and decrease the activation energy. An alternative mechanism for olefin oxidation has been suggested by Swern (*op. cit.*) but this cannot be applied to our reaction, as once again it is ionic.

We therefore regard perbenzoic acid as acting as an electrophilic, molecular (not ionic) reagent in this particular reaction, *i.e.* :



The acid-catalysis noted may be due to protonation of the carbonyl oxygen atom, which facilitates the envisaged electronic shifts. These concepts may profitably be extended to explain the mode of epoxidation of olefins.

The mechanism proposed for the mode of attack of the perbenzoic acid agrees very closely with that recently formulated by Overberger and Cummins (*J. Amer. Chem. Soc.*, 1953, **75**, 4250) for the reaction of perbenzoic acids with 4 : 4'-dichlorobenzyl sulphide.

Grateful acknowledgment is made to Monsanto Chemicals (Australia) Limited for the award of a Research Scholarship to one of us (B. M. L.).

UNIVERSITY, MELBOURNE, N.3, VICTORIA, AUSTRALIA. [*Received, November 24th*, 1953.]

---

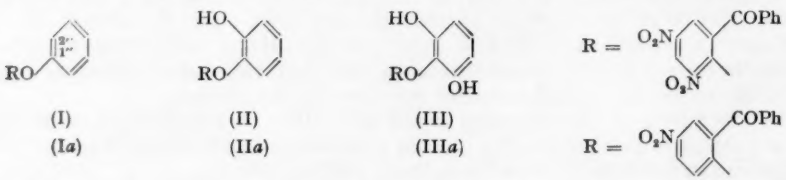
ortho-*Hydroxylation of Phenols. Part IV.* Pyrogallols.*

By J. D. LOUDON and L. A. SUMMERS.

[Reprint Order No. 4874.]

From phenol and its appropriate homologues, *via* 2-aryloxy-3 : 5-dinitrobenzophenones and the derived 2-2''-hydroxyaryloxy- and 2-(2'' : 6''-dihydroxyaryloxy)-3 : 5-dinitrobenzophenones, there are prepared pyrogallol, its 4-methyl, 5-methyl, 4 : 5-dimethyl, and 4 : 6-dimethyl derivatives.

As was shown in Part III * 2-aryloxy-5-nitrobenzophenones (I*a*) may be hydroxylated in successive stages to (II*a*) and (III*a*), but interaction of piperidine with compounds of type (III*a*) causes rearrangement and cyclisation to fluorones instead of scission to pyrogallols. In the hope of securing conditions more favourable to scission, 2-aryloxy-



(I) (I*a*) (II) (II*a*) (III) (III*a*)

3 : 5-dinitrobenzophenones were examined and, with these compounds (I) and their hydroxylation products (II) and (III) as intermediates, the conversion of phenols into the corresponding pyrogallols has now been accomplished.

* Part III, *J.*, 1953, 269.

The greater reactivity of 2-chloro-3 : 5-dinitrobenzophenone over the 5-mononitro-compound enabled diaryl ethers of type (I) to be prepared by reaction with phenols in pyridine at ordinary temperature (cf. Borrows, Clayton, Hems, and Long, *J.*, 1949, S190). Ethers of more sensitive phenols, such as naphthols, and of polyhydric phenols are thereby made available for study (cf. Table 1). Hydroxylation of the dinitro-ethers proceeded

TABLE 1. 2-*Aryloxy*-3 : 5-*dinitrobenzophenones.*

No.	Subst.	M. p.	Formula	Found, % C	Found, % H	Required, % C	Required, % H
I	—	142°	$C_{19}H_{12}O_6N_2$	62·6	3·2	62·6	3·3
IV	3″-Me	159	$C_{20}H_{14}O_6N_2$	63·55	3·9	63·5	3·7
V	4″-Me	130	,,	63·8	3·5	,,	,,
VI	2″ : 5″-Me_2	146	$C_{21}H_{16}O_6N_2$	64·5	3·8	64·3	4·1
VII	3″ : 4″-Me_2	164	,,	64·5	4·3	,,	,,
VIII	3″ : 5″-Me_2	217	,,	64·5	4·2	,,	,,
II	2″-OH	160	$C_{19}H_{12}O_7N_2$	59·9	3·3	60·0	3·2
IX	3″-OH	160—163	,,	60·1	3·2	,,	,,
X	2″ : 3″-Benzo	155	$C_{23}H_{14}O_6N_2$	67·0	3·7	66·7	3·4
XI	3″ : 4″-Benzo	188	,,	66·9	3·0	,,	,,
XII	2″ : 3″-α-Naphtho †	248	$C_{27}H_{16}O_6N_2$	70·0	3·7	69·8	3·5

† From 1-phenanthrol.

essentially as described for the mononitro-ethers (Part II, *J.*, 1953, 265; Part III, *loc. cit.*) but with less allowable latitude in experimental conditions. The restriction is probably imposed by the greater sensitivity of the hydroxylated dinitro-compounds which, in general, are less easily handled and more prone to deterioration on storage. 2-2″-Hydroxyphenoxy-3 : 5-dinitrobenzophenone (II) was alternatively prepared by hydroxylating 2-phenoxy-3 : 5-dinitrobenzophenone (I) and by condensing catechol with 2-chloro-3 : 5-dinitrobenzophenone. It underwent scission when treated with piperidine at room temperature under a variety of conditions, and the products were identified as catechol and 3 : 5-dinitro-2-piperidinobenzophenone. 3 : 6-Dimethylcatechol was also obtained in good yield from 2-(2″-hydroxy-3″ : 6″-dimethylphenoxy)-3 : 5-dinitrobenzophenone (XV) which was prepared *via* the ether (VI) from 2 : 5-dimethylphenol. Scission of the other hydroxyaryloxy-3 : 5-dinitrobenzophenones, listed in Table 2, was not attempted but compounds (XIII) and (XIV) require further comment. Despite their identical m. p.s and the fact that this value is scarcely, if at all, depressed by admixture of the samples, the compounds are quite distinct as is shown by the results of renewed hydroxylation (see Table 3). None the less on methylation by diazomethane in ether they both yielded the same product, namely 2-(2″-methoxy-4″-methylphenoxy)-3 : 5-dinitrobenzophenone, of which the structure was proved in each case by scission with piperidine to 4-hydroxy-3-methoxytoluene. Both compounds are accordingly derived from 3 : 4-dihydroxytoluene but in course of methylation (XIII) undergoes rearrangement to (XIV). Although similar rearrangement has previously been observed under alkaline conditions in the mononitro-series, this is the first instance of its occurrence during methylation by diazomethane.

TABLE 2. 2-2″-*Hydroxyaryloxy*-3 : 5-*dinitrobenzophenones.*

No.	Subst.	Source	M. p.	Formula	Found, % C	Found, % H	Required, % C	Required, % H
II	—	I	160°		see Table I			
XIII	5″-Me	IV	139	$C_{20}H_{14}O_7N_2$	60·85	3·6	60·9	3·55
XIV	4″-Me	V	139	,,	60·95	3·6	,,	,,
XV	3″ : 6″-Me_2	VI	171	$C_{21}H_{16}O_7N_2$	61·8	3·9	61·8	3·9
XVI	4″ : 5″-Me_2	VII	175	,,	62·0	4·1	,,	,,
XVII	3″ : 5″-Me_2	VIII	183 *	,,	61·6	4·0	,,	,,

It recalls the similar methylation of 2-acylalizarin to 1-acylalizarin 2-methyl ether (Perkin and Storey, *J.*, 1928, 229).

Renewed hydroxylation of the compounds of Table 2 was successful in all except (XV) which lacks the requisite free *o*-position. The solid obtained from (XVII) could not be crystallised but subsequent scission showed that it was substantially the expected product.

Scission of the dihydroxy-compounds (Table 3) was much more rapid than in the mono-nitro-series and could be effected at room temperature even in presence of diluents. Tests showed that scission was more reliably achieved by phenylhydrazine than by piperidine—with which fluorone formation was again observed—and the former reagent was accordingly

TABLE 3. 2-(2'' : 6''-*Dihydroxyaryloxy*)-3 : 5-*dinitrobenzophenones.*

					Found, %		Required, %	
No.	Subst.	Source	M. p.	Formula	C	H	C	H
III	—	II	148° *	$C_{19}H_{12}O_8N_2$	57·6	3·3	57·6	3·0
XVIII	3''-Me	XIII	206 *	$C_{20}H_{14}O_8N_2$	58·5	3·4	58·5	3·4
XIX	4''-Me	XIV	164 *	"	58·7	3·6	"	"
XX	3'' : 4''-Me_2	XVI	203 *	$C_{21}H_{16}O_8N_2$	59·7	3·7	59·4	3·8

* Decomp.

adopted. Thereby (III) was smoothly converted into pyrogallol, with 5 : 7-dinitro-1 : 3-diphenylindazole as an easily separable by-product, and by similar means the two monomethyl and the two dimethyl homologues of pyrogallol were prepared.

EXPERIMENTAL

(Petroleum as solvent refers to light petroleum of b. p. 60—80°).

2-*Aryloxy*-3 : 5-*dinitrobenzophenones* (Table 1).—The phenol in slight excess was added to a solution of 2-chloro-3 : 5-dinitrobenzophenone in pure dry pyridine and, after 15 hr., the whole was poured into dilute acid. The resultant solid compounds (I), (IV), (V), (VII), and (VIII) were crystallised from methanol–benzene; (VI) was crystallised from benzene–petroleum; (X) and (XI) from acetic acid; and (XII) from xylene. Compounds (II) and (IX) were crystallised from methanol and were best prepared by using a 6 molar excess of the dihydric phenol in order to minimise formation of di-ethers. *Catechol bis*-(2-*benzoyl*-4 : 6-*dinitrophenyl*) *ether*, m. p. 160° (from acetic acid) (Found : C, 59·3; H, 3·0. $C_{32}H_{18}O_{12}N_4$ requires C, 59·1; H, 2·8%), and *resorcinol bis*(2-*benzoyl*-4 : 6-*dinitrophenyl*) *ether*, m. p. 115° (from acetic acid) (Found, after fusion *in vacuo* : C, 58·9; H, 2·7%), were readily formed when 0·5 molar proportions of the phenols were used.

2-2''-*Hydroxyaryloxy*-3 : 5-*dinitrobenzophenones* (Table 2).—The following is typical : Powdered 3 : 5-dinitro-2-phenoxybenzophenone (0·1 g.) was dissolved in warm concentrated sulphuric acid (0·5 c.c.), and after 30 min. acetic acid (2·5 c.c.) was added. The red solution was allowed to cool and was then titrated with a solution of 30% hydrogen peroxide in acetic acid (1 : 2 by vol.) until a slight excess of the oxidising agent was present. After 15—30 min., when the colour of the solution had faded to amber and in some cases the product had crystallised, the whole was stirred into crushed ice, and the resultant solid crystallised from methanol. Compounds (XV), (XVI), and (XVII) were crystallised from methanol, ethanol, and aqueous ethanol, respectively; compounds (XIII) and (XIV) from benzene–petroleum and, as frequently observed with these solvents, the crystals retained solvent which was removed at 125° *in vacuo*. On one occasion compound (XIII) was obtained with m. p. 159° (from benzene–petroleum) changing to m. p. 146° when kept *in vacuo* at 125° (Found : C, 61·05; H, 3·8%).

2-(2'' : 6''-*Dihydroxyaryloxy*)-3 : 5-*dinitrobenzophenones* (Table 3).—Acetic acid (3·5 c.c.) was added to the monohydroxy-compound (0·1 g.) in concentrated sulphuric acid (0·5 c.c.), affording dark red-brown solutions from (II) and (XIV), and dark green solutions from (XIII), (XVI), and (XVII). After titration with a slight excess of the hydrogen peroxide–acetic acid solution, the colour changed to amber within 10 min., and the whole was at once added to ice. The products crystallised with difficulty, deteriorating in hot solution and retaining (hydrocarbon) solvents in the crystals. For analysis (III) was crystallised from acetic acid–petroleum; (XVIII) from chloroform; (XIX) from benzene, with subsequent heating at 140° *in vacuo*; and (XX) from methanol. Hydroxylation of (XVII) (0·1 g.) was best effected by using increased quantities of sulphuric (3 c.c.) and acetic (10 c.c.) acids, but the product, although a solid, could not be crystallised and was directly used for scission to 4 : 6-dimethylpyrogallol.

Scissions.—With piperidine. 3 : 5-Dinitro-2-phenoxybenzophenone (I) and piperidine reacted vigorously alone and, more slowly, in solution in cold benzene even in presence of acetic acid equivalent to the quantity of amine used. After several hours, in all three cases phenol was recovered in alkali from a solution of the products in benzene and was identified as tribromophenol. The residual benzene solution, when acid-washed, dried and concentrated, and the concentrate treated with petroleum, afforded 3 : 5-*dinitro*-2-*piperidinobenzophenone*

as orange plates, m. p. 125° (from ethanol), also prepared from piperidine and 2-chloro-3 : 5-dinitrobenzophenone (Found : C, 60·9; H, 5·0. $C_{18}H_{17}O_5N_3$ requires C, 60·8; H, 4·8%). In corresponding experiments with (II) in place of (I) catechol was isolated, being recovered in ether after saturation of the acidified alkaline extract with ammonium sulphate, and was purified by sublimation.

When treated (48 hr.) with diazomethane in ether, compound (XIV) afforded 2-(2″-*methoxy*-4″-*methylphenoxy*)-3 : 5-*dinitrobenzophenone*, m. p. 186°, from benzene–petroleum (Found : C, 62·0; H, 4·0. $C_{21}H_{16}O_7N_2$ requires C, 61·8; H, 3·9%), and the same compound, m. p. and mixed m. p. 186—187°, was likewise produced from (XIII). In separate experiments a sample of the product (1 mol.) from each source was suspended in benzene, treated with piperidine (3 mol.) and, after 15 hr., the resultant solution was extracted with aqueous sodium hydroxide from which by acidification, saturation with ammonium sulphate, and recovery in ether, 4-hydroxy-3-methoxytoluene was obtained as an oil. In each case the scission product was identified as the picrate, (micro-) m. p. 104° (cf. Part I; *J.*, 1950, 55), and benzoate, m. p. 72° (Cosgrove and Waters, *J.*, 1949, 3189, give m. p. 73°) (the picrate and benzoate of 3-hydroxy-4-methoxytoluene have m. p.s 87·5° and 81°, respectively).

A solution of (III) (1 mol.) in benzene and piperidine (4 mol.) was extracted after 24 hr. with aqueous sodium hydroxide which, on acidification, afforded 4-*hydroxy*-5 : 7-*dinitro*-9-*phenylfluorone* as black crystals, m. p. (decomp.) 335° (from anisole : they were ground under methanol before analysis) (Found : C, 60·45; H, 2·9. $C_{19}H_{10}O_7N_2$ requires C, 60·3; H, 2·65%). When a large excess of piperidine was used neither the fluorone nor pyrogallol could be obtained from the alkaline extract, but the residual benzene solution afforded 3 : 5-dinitro-2-piperidinobenzophenone.

With hydroxylamine. A solution of (III) (1 mol.) and hydroxylamine (1 mol.; from the hydrochloride and sodium acetate) in methanol was filtered after 3 hr. from the crystalline precipitate of 5 : 7-dinitro-3-phenylbenz*iso*oxazole (m. p. 244°, from benzene, undepressed by admixture with a sample prepared as described by Meisenheimer, Zimmerman, and Kummer, *Annalen*, 1925, **446**, 205), and the filtrate was diluted with ether. The ethereal solution, successively washed with aqueous sodium carbonate, dilute acid, and water, was dried and concentrated. Sublimation of the residue at 20 mm. afforded pyrogallol, m. p. 126° raised to 128—130° by admixture with an authentic sample. The yield was poor.

With phenylhydrazine. A solution of the compound (1 mol.) and phenylhydrazine (5 mol.) in benzene was kept for 15 hr. It was then extracted with dilute sodium hydroxide, and the aqueous layer immediately run into dilute sulphuric acid. The acid solution was saturated with ammonium sulphate and exhausted with ether. The material recovered from the dried ethereal solution was sublimed at 20 mm. and the phenolic sublimate was further purified as required. The residual benzene solution contained 5 : 7-dinitro-1 : 3-diphenylindazole which, after the excess of phenylhydrazine was washed out by aqueous acetic acid, was recovered as plates, of m. p. 218°, from ethanol, m. p. undepressed by admixture with an authentic sample (Borsche and Scriba, *Annalen*, 1939, **540**, 83) (Found : C, 63·3; H, 3·5. Calc. for $C_{19}H_{12}O_4N_4$: C, 63·3; H, 3·3%). The following were thus prepared : Catechol, m. p. and mixed m. p. 105°, from benzene–petroleum; from (II). 3 : 6-Dimethylcatechol, needles (from benzene–petroleum), m. p. 102° undepressed with a sample prepared as in Part II (*loc. cit.*); from (XV).

Pyrogallol, m. p. and mixed m. p. 132°, from benzene; from (III).

4-Methylpyrogallol, m. p. 142°, from benzene–petroleum; from (XVIII) (Found : C, 60·1; H, 5·8. Calc. for $C_7H_8O_3$: C, 60·0; H, 5·7%). Majima and Okasaki (*Ber.*, 1916, **49**, 1492) give m. p. 140—141°.

5-Methylpyrogallol, m. p. 120°, from benzene; from (XIX) (Found : C, 60·2; H, 5·9%). Recorded m. p.s range from 119 to 129°.

4 : 5-*Dimethylpyrogallol*, m. p. 148°, from benzene; from (XX) (Found : C, 62·6; H, 6·6. $C_8H_{10}O_3$ requires C, 62·3; H, 6·5%).

4 : 6-Dimethylpyrogallol, m. p. and mixed m. p. 122—123° (Part III; *loc. cit.*); from the solid hydroxylation product of (XVII).

We gratefully acknowledge our indebtedness to the Department of Scientific and Industrial Research for a Maintenance Allowance (to L. A. S.) and to Messrs. W. P. Hamill and J. A. Scott for some helpful preliminary work. Microanalyses were carried out by Mr. J. M. L. Cameron and Miss M. W. Christie.

UNIVERSITY OF GLASGOW. [*Received, December 9th*, 1953.]

The Liquid Dinitrogen Tetroxide Solvent System. Part XVI. Reactions with Ethylammonium Nitrate Solutions: Ethylammonium Tetranitratozincate.*

By C. C. Addison and N. Hodge.

[Reprint Order No. 4626.]

The reaction of solutions of ethylammonium nitrate in liquid dinitrogen tetroxide with metallic zinc gives a crystalline product, $Zn(NO_3)_2,2EtNH_3NO_3$. Properties of this compound, and of its solutions in nitromethane, liquid dinitrogen tetroxide, and hydroxylic and other solvents are described. Conductivity and electrolytic measurements indicate that the compound may be formulated as $(EtNH_3^+)_2[Zn(NO_3)_4]^{2-}$. Ethylammonium salts undergo some decomposition in liquid dinitrogen tetroxide, and this side reaction has also been studied.

Compounds which give rise to "basic" solutions in liquid dinitrogen tetroxide fall into two types. The first type (typified by diethylnitrosamine) enhances the ionisation $N_2O_4 \rightleftharpoons NO^+ + NO_3^-$ by formation of addition compounds with the NO^+ ion (*J.*, 1952, 1390, 1399). Compounds of the second type (typified by the alkylammonium nitrates) introduce the nitrate ion directly into the system. Solutions of compounds of each type attack metals more rapidly than does dinitrogen tetroxide alone, and from solutions of the second type it is possible to separate crystalline reaction products. The product of reaction of monoethylammonium nitrate with zinc, obtained over a wide range of experimental conditions, may be represented as $(EtNH_3)_2[Zn(NO_3)_4]$, and contains no combined dinitrogen tetroxide. The present paper describes the preparation and the properties of this compound, together with some properties of other closely related compounds, such as $(NO)_2[Zn(NO_3)_4]$ and anhydrous zinc nitrate, which have not already been described but have direct significance in the study of ethylammonium tetranitratozincate. The reaction products obtained by using di-, tri-, and tetra-ethylammonium nitrate solutions contain an amount of combined dinitrogen tetroxide which varies with conditions (*J.*, 1954, 1143).

Mixtures of ethylammonium nitrate and dinitrogen tetroxide containing up to 58% of the former separate into two liquid phases immediately on being mixed. The upper phase contains all the nitrate and some dinitrogen tetroxide, the lower layer being pure tetroxide. Concentrated solutions containing more than 58% of the nitrate consist of one liquid phase only. A side reaction occurs between the components of the mixture, but not to a sufficient extent to complicate the metal–solution reactions reported here.

Reaction with Metallic Zinc.—When a block of zinc was suspended in the upper layer of an ethylammonium nitrate–dinitrogen tetroxide mixture, reaction was immediate, but the rate varied widely with temperature. At 0° the green colour of dinitrogen trioxide was perceptible only after 2 hr., although above 20° reaction was vigorous, with effervescence of nitric oxide. Although the reaction rate is much greater than with dinitrogen tetroxide alone, its variation with temperature follows the same course as with the pure tetroxide (Part VIII, *J.*, 1951, 2833), where the rate of the electron-transfer reaction $Zn + 2[NO^+][NO_3^-] = Zn(NO_3)_2 + 2NO$ is limited by the very low concentration of ion-pairs. The polar nature of added ethylammonium nitrate will increase the dielectric constant of the medium, the concentration of NO^+ ions, and the rate of reaction. In reaction with tetroxide alone, the insoluble product $(NO)_2[Zn(NO_3)_4]$ is formed, whereas in the presence of ethylammonium nitrate this initial product reacts to form a soluble complex.

On continued reaction, the product accumulated exclusively in the upper layer until the density of this layer exceeded that of dinitrogen tetroxide, whereupon inversion occurred. With an 11·5% solution inversion took place after 2 hr. at room temperature. Small needle crystals which separated from the lower layer after a further hour were shown

* Part XV, *J.*, 1953, 2631.

by analysis to contain no nitrite or combined dinitrogen tetroxide, and to contain zinc, ethylamine, and the nitrate ion in the ratio 1 : 2 : 4. On the basis of properties described below, the compound is formulated as $(EtNH_3)_2[Zn(NO_3)_4]$, and is produced by the acid–base reaction

$$(NO^+)_2[Zn(NO_3)_4]^{2-} + 2EtNH_3^+NO_3^- = (EtNH_3^+)_2[Zn(NO_3)_4]^{2-} + 2N_2O_4 \quad . \quad . \quad (1)$$

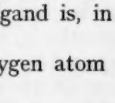
This reaction illustrates the amphoteric behaviour of zinc salts in dinitrogen tetroxide medium, and the equations

$$Zn + 2EtNH_3NO_3 + 2N_2O_4 = (EtNH_3)_2[Zn(NO_3)_4] + 2NO$$
$$Zn + 2NaNH_2 + 2NH_3 = Na_2[Zn(NH_2)_4] + H_2$$
$$Zn + 2NaOH + 2H_2O = Na_2[Zn(OH)_4] + H_2$$

relate similar properties of zinc in the three solvent systems.

4-Co-ordinate complexes containing nitrate groups only are little known; Jander and Wendt (*Z. anorg. Chem.*, 1949, **258**, 1) found that the solubility of cadmium nitrate in pure nitric acid is increased on addition of potassium nitrate, and a similar nitrato-complex may be formed. The formation of such complexes in aqueous medium is improbable, since the equilibria

$$[Zn(NO_3)_4]^{2-} \rightleftharpoons [Zn(H_2O)_4]^{2+} \text{ or } (Zn(NO_2)_4]^{2-} \rightleftharpoons [Zn(OH)_4]^{2-}$$

will be displaced far in the forward direction. The nitrato-uranyl complexes are similarly unstable in hydroxylic solvents (Addison and Hodge, *Nature*, 1953, **171**, 569). With ligands containing nitrogen and oxygen atoms, the ligand is, in general, preferentially co-ordinated through the nitrogen rather than the oxygen atom (hence  is a more stable co-ordinating group than ←O·N=O⁻); but with the nitrate ion co-ordination is necessarily with an oxygen atom since the nitrogen atom has no available electron pair, and the formation of nitrato-complexes is therefore only likely in media (such as nitric acid or dinitrogen tetroxide) which provide no competing ligands.

Properties of Ethylammonium Tetranitratozincate.—The compound is extremely deliquescent, necessitating transfer and manipulation in a closed system. The properties of its solutions vary with the solvent used.

(a) *Nitromethane.* This is an excellent solvent for the compound. Anhydrous zinc nitrate dissolves slowly in it (solubility 0·025M), but more rapidly, and to a greater extent, in the presence of ethylammonium nitrate, its solubility being 0·055M in a 0·064M-solution, *i.e.*, the increase in quantity of dissolved zinc nitrate is nearly that required to convert ethylammonium nitrate into the tetranitratozincate.

(b) *Liquid dinitrogen tetroxide.* The compound is insoluble in this medium; on prolonged immersion the crystals became partially liquefied, forming a separate yellow, viscous phase. (When the tetroxide was removed in a current of dry air the original compound was recovered.) Analysis showed the viscous liquid to contain an excess of ethylammonium nitrate whereas the crystals contained an excess of zinc nitrate. These observations may be interpreted by reference to equation (1). The equilibrium lies largely to the right, but the reverse reaction accounts for the degeneration of the crystals. Equilibrium is rapidly produced in the forward direction; when the equivalent quantity of liquid ethyl ammonium nitrate was added to the compound $(NO)_2[Zn(NO_3)_4]$, free liquid dinitrogen tetroxide was immediately produced, which could be decanted to leave the equilibrium mixture.

(c) In benzene, ether, dioxan, carbon tetrachloride, and chloroform the crystals were insoluble, and showed no physical or chemical change on prolonged immersion.

(d) *Ketonic solvents.* With acetone and *cyclo*hexanone, a colourless solution was obtained, which became brown on storage. The absorption spectrum of a fresh solution in *cyclo*hexanone (given below) shows no characteristic feature over the available range.

λ, mμ	340	350	360	370	390	410	430	450	470	490
ε	9·09	6·27	3·56	2·13	1·07	0·64	0·47	0·38	0·31	0·28

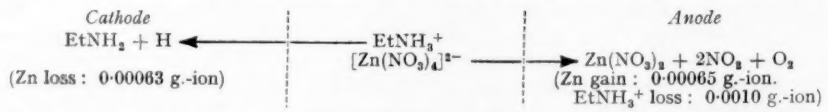
(e) *Hydroxylic solvents.* The compound dissolves readily in water and absolute alcohol, but dissociates as follows:

$$(EtNH_3)_2[Zn(NO_3)_4] = 2EtNH_3^+ + Zn^{2+} + 4NO_3^-$$

The ultra-violet absorption spectrum of the aqueous solutions shows a peak characteristic of the nitrate ion at 304 mμ; $\varepsilon_{max.} = 7{\cdot}06$ being assumed, then the concentration of free nitrate ions in the solution, calculated from the absorption curve, is in exact agreement with the above equation. The spectrum of the solution in absolute alcohol shows a peak at 300 mμ and $\varepsilon_{max.} = 5{\cdot}79$. The value of $\varepsilon_{max.}$ for the nitrate ion in absolute alcohol (determined with a solution of ammonium nitrate) is 6·3, so that the compound is largely, if not completely, dissociated in absolute alcohol also.

Action of Heat.—The compound melted sharply at 83—84° without decomposition, giving a colourless liquid. Between 190° and 210° the melt changed to deep yellow brown, with slight decomposition. At 220° the compound decomposed rapidly but quietly, with 45% loss in weight. At 270° a vigorous decomposition occurred, leaving a white solid which was mainly zinc oxide. The decomposition occurring at 190—220° is probably due to ethylammonium nitrate, which decomposes over the same temperature range. The decomposition at 270° involves thermal disruption of the nitrate group, and oxidation of the remaining organic material. When a sample was heated rapidly to 270°, without delay at 190—220°, decomposition was explosive and the gaseous products ignited.

Electrolysis of Solutions.—Electrolysis was carried out at 20° in a three-compartment cell. The electrode compartments had a capacity of 36 ml., the total capacity being 95 ml. Bright platinum electrodes were used. From a 4% solution of ethylammonium tetranitratozincate in nitromethane, oxygen gas was liberated from the anode. When the platinum anode was replaced by zinc, no gas evolution occurred. The zinc became coated with zinc oxide, and zinc nitrate was eventually precipitated from the solution. Analysis of the cathode compartment showed a decrease in zinc content, indicating the presence of zinc in the anion. The electrolysis was studied quantitatively by use of an iodine coulometer. A 4·23% solution was electrolysed for 9 hr. at 220 v p.d., and 0·00216 F was passed, and the changes in concentration in the cathode and the anode compartment compared with those expected on the assumption that ethylammonium tetranitratozincate ionises in nitromethane solutions of this concentration into $EtNH_3^+$ and



$[Zn(NO_3)_4]^{2-}$ ions only. The transport number of the $EtNH_3^+$ ion (t_+) is 0·0010/0·00216 = 0·46. Similarly, the transport number of the $[Zn(NO_3)_4]^{2-}$ ion (t_-) is 0·00126/0·00216 = 0·58. The fact that $t_+ + t_- = 1{\cdot}04$ suggests that no other ions make a significant contribution to the transport of current.

The above effects have been compared with those observed on electrolysis of a 0·7% solution of the compound $(NO)_2[Zn(NO_3)_4]$ in nitromethane. The presence of the NO^+ ion in solution was shown by a green colour round the cathode, with evolution of nitric oxide. The solution, and the atmosphere above it, contained appreciable quantities of dinitrogen tetroxide, so the equilibrium $(NO^+)_2[Zn(NO_3)_4]^{2-} \rightleftharpoons Zn(NO_3)_2 + 2N_2O_4$ exists in the solution. Oxygen was evolved from the anode by the discharge of NO_3^- or $[Zn(NO_3)_4]^{2-}$ ions, and reversal of the current discharged the green colour round the cathode. No zinc was deposited on the cathode; it was probably dissolved, as soon as deposited, by the dinitrogen trioxide and tetroxide in the solution (Part IX, *J.*, 1951, 2838).

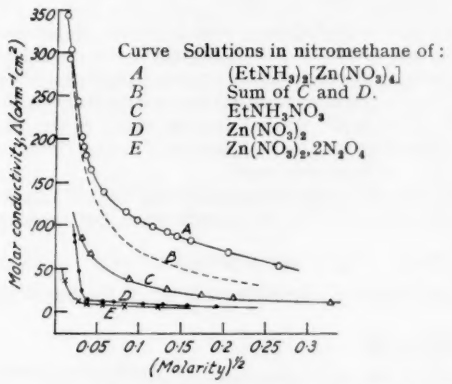
Conductometric Experiments.—The molar conductivity of solutions of zinc nitrate and ethylammonium nitrate in nitromethane at 20° has been determined over a concentration range, and the results are shown graphically in Fig. 1, together with values for solutions of the compounds $Zn(NO_3)_2{,}2N_2O_4$ and $(EtNH_3)_2[Zn(NO_3)_4]$. None of the Λ–$\sqrt{M}$ curves approaches linearity, and all the solutes are weak electrolytes in nitromethane (cf. Walden and Birr, *Z. phys. Chem.*, 1932, **163**, 263; Wynne-Jones, *J.*, 1931, 795). The conductivity

values shown in curves *D* and *E* cannot be read with accuracy from Fig. 1 and are given below :

Molar concn. × 10^4	1·36	3·27	9·9	13·6	30·7	68·0	102	153
Molar conductivity, ohm^{-1} $cm.^2$								
$Zn(NO_3)_2$	—	—	22·6	13·8	10·6	9·5	8·8	7·9
$Zn(NO_3)_2,2N_2O_4$	36·0	17·9	11·2	9·9	8·4	7·4	6·8	6·3

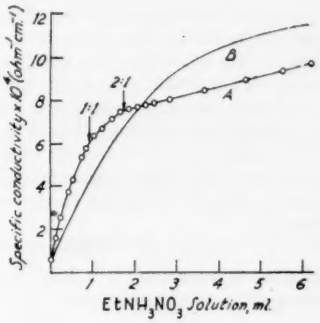
The magnitude of these values, and the shape of the curves, indicate that ionic dissociation is small. The similarity in the values is not significant, since differing degrees of dissociation may be balanced by the difference in the mobilities of the ions concerned. Curve *B* is obtained by summation from curves *C* and *D*, and represents the conductivity of a solution containing ethylammonium nitrate and zinc nitrate in the molar ratio 2 : 1, assuming that no complex ion formation occurs. Curves *B* and *A* coincide at high dilution; this is consistent with a shift in the equilibrium $[Zn(NO_3)_4]^{2-} \rightleftharpoons Zn^{2+} + 4NO_3^-$ towards the right-hand side with decreasing concentration. The fact that curve *A* shows the highest conductivity values may be attributed to a smaller degree of association between the ions $EtNH_3^+$ and $[Zn(NO_3)_4]^{2-}$. With ethylammonium salts of simple anions association of the hydrogen of the cation with the anion is known to be pronounced, and in

FIG. 1.



Curve Solutions in nitromethane of :
A $(EtNH_3)_2[Zn(NO_3)_4]$
B Sum of *C* and *D*.
C $EtNH_3NO_3$
D $Zn(NO_3)_2$
E $Zn(NO_3)_2,2N_2O_4$

FIG. 2.



the compound $(NO)_2[Zn(NO_3)_4]$ strong association between the NO^+ groups and the nitrate groups in the cation will result in low conductivity values.

Curve *A*, Fig. 2, shows the titration curve obtained when a 1·56% solution of ethylammonium nitrate in nitromethane was added progressively to a solution of 0·0386 g. of zinc nitrate in 10 ml. of nitromethane at −15°. At a molecular ratio of 1 : 1 the curve shows a change in direction, and at 2 : 1 a sharp break occurs. Up to the 2 : 1 ratio, the weakly conducting salt $Zn(NO_3)_2$ is replaced by the more strongly conducting $(EtNH_3)_2[Zn(NO_3)_4]$. The departure from linearity is attributed to decrease in the degree of dissociation of the ion $[Zn(NO_3)_4]^{2-}$, whose concentration varies widely over this range. Beyond the 2 : 1 ratio, no change in conducting species is involved, and the slow increase in conductivity is due only to changing concentration of ethylammonium nitrate. Curve *B*, Fig. 2, was obtained when titrating a corresponding solution of the compound $(NO)_2[Zn(NO_3)_4]$. The N_2O_4–$EtNH_3NO_3$ reaction gives highly conducting products, which mask the break in the curve which would otherwise occur.

EXPERIMENTAL

Reaction of Ethylammonium Salts with Dinitrogen Tetroxide.—A weighed quantity of the nitrate (Table 1) was treated with dinitrogen tetroxide. After reaction, the tetroxide and readily volatile products were removed under reduced pressure, and the product weighed. The percentage increase in weight (col. 7) is a suitable measure of the extent of reaction.

TABLE 1.

Expt. No.	Wt. of $EtNH_3NO_3$ (g.)	Conditions of soln. in N_2O_4	Duration of reaction (hr.)	Temp.	Wt. of product (g.)	Increase in wt., %	HNO_3 produced (g.)
1	1·1720	8 g. N_2O_4 (two layers)	4	0°	1·1729	0·08	—
2	0·9727	8 g. N_2O_4 (two layers)	30	20	0·9974	2·54	—
3	0·7810	80% concn. in N_2O_4 (one phase)	30	20	0·9096	16·46	0·219

In its reaction with diethylammonium nitrate (Part V, *J.*, 1951, 1298) the behaviour of the N_2O_4 molecule is analogous to that of nitrous acid (NO·OH). With the monoethyl compound, it would be represented by

$$EtNH_2NO_3 + NO{\cdot}NO_3 = EtOH + N_2 + 2HNO_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Under conditions which give more rapid reaction (Expt. 3) bubbles of an insoluble gas were produced, and a deep green-blue colour developed in the liquid, owing to subsequent reaction of ethyl alcohol. Yoffe and Gray (*J.*, 1951, 1412) find the reaction to occur largely as

$$EtOH + N_2O_4 = EtO{\cdot}NO + HNO_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

but under the different conditions used in this work, the alternative reactions

$$EtOH + N_2O_4 = EtNO_3 + HNO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

$$2EtOH + N_2O_4 = EtNO_2 + EtNO_3 + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

must be considered as occurring also. Comparison of Expts. 1 and 2 (Table 1) shows the increase of reaction rate with temperature, and expts. 2 and 3 illustrate the considerable increase in rate when the two components form one homogeneous phase. Reactions of these solutions with metallic zinc were carried out at ethylammonium nitrate concentrations below 58%, and were normally completed within 4—6 hr. at 20°, so that decomposition of the nitrate was not significant, although it does no doubt account for the high electrical conductivity (κ = 10^{-3}—10^{-4} ohm^{-1} cm.$^{-1}$) of the upper liquid layer in these mixtures.

Reaction with nitrosyl chloride is analogous to that with dinitrogen tetroxide. When ethylammonium chloride is added to the tetroxide, solvolysis occurs immediately; the subsequent reaction

$$EtNH_2NO_3 + NOCl = EtOH + N_2 + HCl + HNO_3 \quad . \quad . \quad . \quad . \quad . \quad (6)$$

is analogous to equation (2). Table 2 gives the results of experiments in which the liquid phase contained nitrosyl chloride also.

TABLE 2.

Expt. No.	Wt. of $EtNH_3Cl$ (g.)	Duration of reaction (hr.)	Temp.	Wt. of product (g.)	Increase in wt., %	Analysis of product: HNO_3 (g.)	Analysis of product: $EtNH_3NO_3$ (g.)
4	2·83	10	−5° to +20°	4·00	6·10	—	—
5	6·11	8	−10° to +20°	8·42	3·95	—	—
6	8·89	6	−15° to 0°	11·84	0·40	—	—
7	2·263	4·75	20°	3·110	3·67	0·162	—
8	1·612	6	20°	2·271	6·28	0·220	1·980
9	0·935	3·25	20°	1·280	3·50	0·094	1·171

In Expts. 4—6, gentle suction was applied to remove nitrosyl chloride immediately after dissolution of the ethylammonium chloride, so the nitrosyl chloride was present in diminishing quantity. The low temperature was maintained by evaporation of solvent, but rose gradually during the experiment. The % weight increase (col. 6) is calculated on the basis of the weight of ethylammonium nitrate equivalent to the quantity of chloride used. Expts. 4—6 show clearly the pronounced decrease in decomposition rate which results from decrease in temperature. In Expts. 7—9 the nitrosyl chloride was not removed from the solution, and these experiments may be compared directly with Expts. 1—3 to show the greater rate at which nitrosyl chloride causes decomposition of ethylammonium nitrate.

Analysis of the product gave the number of moles of nitric acid produced from the decomposition of each mole of ethylammonium nitrate. Equations (2) and (3) require a $HNO_3/EtNH_3NO_3$ ratio of 3; equations (6) and (3) require a ratio of 2. The results of Expts. 8 and 9 are in close agreement, with ratios of 2·36 and 2·33, respectively.

Preparation of Pure Ethylammonium Nitrate.—Slightly more than the theoretical quantity of dinitrogen tetroxide was added at −20° to about 10 g. of dry ethylammonium chloride.

Suction was applied immediately on mixing to remove nitrosyl chloride and excess of dinitrogen tetroxide; the resulting liquid was dissolved in absolute alcohol, and dry ether added at −30°. The precipitate was filtered off rapidly at this temperature and washed with cold ether, and the ether removed under reduced pressure below 0°. The product had m. p. 12° (cf. 8°, Sugden and Wilkins, *J.*, 1929, 1297; 13—14°, Walden, *Chem. Zentr.*, 1914, I, 1800) (Found: $EtNH_2$, 41·5. Calc. for $EtNH_3NO_3$: $EtNH_2$, 41·68%).

Product of Reaction with Zinc.—The impure crystals were filtered on a Grade 2 sintered-glass filter tube. After purification of the product (outlined below), the crystals were dissolved in water; the zinc content was determined by means of 8-hydroxyquinoline, and the amine content by addition of alkali and distillation into standard acid. Nitrate was determined in the solution remaining after distillation by use of Devarda's alloy. Analytical results are given in Table 3: all results are referred to 1 g.-atom of zinc.

TABLE 3.

Prepn. No.	Zn (g.-atoms)	$EtNH_3^+$ (g.-ions)	NO_3^- (g.-ions)	N_2O_4 (mole)
1	1·0	1·82	3·79	0·125
2	1·0	2·20	4·20	—
3	1·0	1·99	4·00	—

Prepn. 1 was carried out by reaction of a 5-g. block of zinc with a solution of 3·8 g. of ethylammonium nitrate in 25 ml. of dinitrogen tetroxide for 10 hr. On filtration and suction, the product gave dry crystals, but the analytical results show that these conditions gave a product contaminated with the compound $(NO)_2[Zn(NO_3)_4]$. In prepn. 2 the concentration was increased (6·6 g. of ethylammonium nitrate in 20 ml. of tetroxide) and the reaction time reduced to 4 hr. Passage of dry air for 30 min. through the mat of crystals removed all the tetroxide, leaving a dry powder (analysis 2). Under these conditions the product is therefore contaminated with ethylammonium nitrate. Prepn. 3 was carried out as described for prepn. 2, but the product was washed with nitromethane (in which ethylammonium nitrate dissolves more rapidly) before analysis. The results (analysis 3) confirm the preparation of the pure *compound* $(EtNH_3)_2[Zn(NO_3)_4]$.

Conductivity Measurements.—These were carried out in an apparatus similar to that described in Part XV (*loc. cit.*).

THE UNIVERSITY, NOTTINGHAM. [*Received, September 2nd*, 1953.]

NOTES.

The Liquid Dinitrogen Tetroxide Solvent System. Part XVII. The Equilibrium between Alkylammonium and Nitrosonium Tetranitratozincates.*

By C. C. ADDISON, N. HODGE, and R. THOMPSON.

[Reprint Order No. 4627.]

THE liquid obtained on dissolving zinc in a solution of alkylammonium nitrate in liquid dinitrogen tetroxide contains the anion $[Zn(NO_3)_4]^{2-}$; the corresponding cations are NR_4^+ and NO^+. The salt which separates on crystallisation from these solutions varies with the nature of the group NR_4^+. The results may be interpreted in terms of an equilibrium

$$(NR_4)_2[Zn(NO_3)_4] + 2N_2O_4 \rightleftharpoons (NO)_2[Zn(NO_3)_4] + 2NR_4NO_3 \quad . \quad . \quad . \quad . \quad (1)$$

When NR_4^+ is the ethylammonium ion, the equilibrium is displaced towards the left-hand side (Part XVI, *loc. cit.*). As the number of ethyl groups in the NR_4^+ ion is increased, the equilibrium is displaced progressively towards the right-hand side.

Reaction with Diethylammonium Nitrate Solutions.—Reaction commenced immediately on addition of zinc to the homogeneous solution. Nitric oxide was evolved, and a green, viscous liquid rose from the zinc block in globules to form an upper phase. As reaction proceeded, the volume of the upper layer increased, and the diethylammonium nitrate concentrated in this

* Part XVI, *J.*, 1954, 1138.

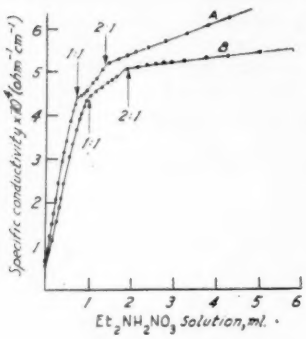
layer, leaving a lower layer consisting of almost pure dinitrogen tetroxide. When sufficient zinc dissolved the layers became inverted and crystallisation occurred from the lower layer. With a 9% solution the layers were inverted after 10 hr., and crystallisation commenced after a further 8 hr. The product formed fine, needle-shaped crystals which contained diethylamine, zinc, nitrate, and combined dinitrogen tetroxide, but the diethylamine : zinc ratio falls considerably below that required by the formula $(Et_2NH_2)_2[Zn(NO_3)_4]$. The analysis varies with the concentration of the diethylammonium nitrate solution from which the product was crystallised. The analyses in Table 1 are calculated on the basis of 1 g.-atom of zinc. The

TABLE 1.

NO_3^- (g.-ions)	$Et_2NH_2^+$ (g.-ions)	N_2O_4 (mols.)	NO_3^- (g.-ions)	$Et_2NH_2^+$ (g.-ions)	N_2O_4 (mols.)	NO_3^- (g.-ions)	$Et_2NH_2^+$ (g.-ions)	N_2O_4 (mols.)
2·41 (4·25)	0·205	1·84	2·50 (4·25)	0·41	1·75	2·66 (4·08)	0·62	1·42
2·24 (4·12)	0·235	1·88	—	0·44	1·68	2·39 (3·69)	0·62	1·30
2·32 (4·10)	0·265	1·78	2·37 (3·78)	0·56	1·41	2·50 (3·93)	0·65	1·43
2·32 (3·99)	0·375	1·67						

results are consistent if it is assumed that all the N_2O_4 molecules exist in the compound in the form of NO^+ and NO_3^- ions, and that the latter are combined in the $[Zn(NO_3)_4]^{2-}$ ion. The numerals in parentheses in col. 1 then give the total number of NO_3^- ions associated with each g.-atom of zinc, and the mean Zn : NO_3 ratio is 1 : 4·02.

If isomorphous replacement of NO^+ by $Et_2NH_2^+$ in the crystals is excluded because of difference in ionic size, the products may be regarded as mixtures of the compound $(NO)_2[Zn(NO_3)_4]$ with either $(Et_2NH_2)_2[Zn(NO_3)_4]$ or an " acid " salt $(Et_2NH_2)_x(NO)_y[Zn(NO_3)_4]$ of definite composition. In spite of the wide variations in $Et_2NH_2^+$ and NO^+ content, their sum is constant within experimental error (mean total 2·05 g.-ions, limits 1·92—2·16 g.-ions) which excludes the presence of the separate components N_2O_4, $Zn(NO_3)_2$, and $Et_2NH_2NO_3$. Attempts to obtain crystals containing an amine content above the range shown in Table 1 (by use of solutions containing up to 60% of diethylammonium nitrate) resulted in formation of a viscous liquid from which no crystalline product could be separated. Therefore, although the compound $(Et_2NH_2)_2[Zn(NO_3)_4]$ may be capable of preparation by other methods, a compound in which the $Et_2NH_2^+$: NO^+ ratio is 0·65 : 1·35 represents the limit in the presence of liquid dinitrogen tetroxide. Thus when up to about 0·65 mole of solid diethylammonium nitrate was added to 1 mole of the compound $(NO)_2[Zn(NO_3)_4]$ an equivalent quantity of liquid dinitrogen tetroxide could be decanted from the crystalline product. The addition of greater quantities of diethylammonium nitrate did not appreciably increase the yield of dinitrogen tetroxide. The product liquefied immediately on heating, and all dinitrogen tetroxide could be removed at 100°. At 160° the clear liquid decomposed vigorously, evolving fumes containing nitrogen dioxide, diethylnitrosamine, and nitric acid, and leaving a solid residue of zinc oxide, zinc nitrate, and charred organic matter. At 210° (the temperature at which zinc nitrate begins to decompose) a second vigorous reaction occurred, in which organic matter was oxidised and pure zinc oxide remained. Electrolysis of solutions of the product in both nitromethane and nitrobenzene confirmed the presence of the NO^+ ion in these solutions. Analyses of the contents of the anode and cathode compartments indicated migration of zinc to the anode.



The Figure shows conductometric titration curves obtained on the addition of a 1·8% solution of diethylammonium nitrate (in nitromethane) to 10 ml. of a 0·164% zinc nitrate solution at 0° (curve *A*) or of a 0·247% solution at −15° (curve *B*). The arrows indicate the points on the curves at which the ratio $Et_2NH_2NO_3$: $Zn(NO_3)_2$ is 1 : 1 and 2 : 1. As with the monoethyl compound, there is a pronounced break at the 2 : 1 ratio in each curve, although no such break is obtained in the presence of dinitrogen tetroxide. In this system, however, the break in the curves at the 1 : 1 ratio is much more pronounced. This may be compared with observations by Nayar and Pande (*J. Indian Chem. Soc.*, 1951, **28**, 107; *Proc. Indian Acad. Sci.*, 1949, **30**, *A*, 251) on the formation of complex compounds between lead nitrate and the alkali-metal nitrates in aqueous solution.

Reaction with Triethylammonium Nitrate Solutions.—Fresh solutions form a single liquid

phase over the full concentration range, and only separate into two phases very slowly (*e.g.*, after 10 hr. with a 5% solution). Reaction with zinc follows the same course as with the diethyl compound, but is more rapid. The product quickly crystallised in fine needles (after 30 min. when a 7% solution was used) which were readily filtered off. Table 2 gives analytical results on separate preparations (calculated on the basis of 1 g.-atom of zinc).

TABLE 2.

NO_3^- (g.-ions)	Et_3NH^+ (g.-ions)	N_2O_4 (mols.)	NO_3^- (g.-ions)	Et_3NH^+ (g.-ions)	N_2O_4 (mols.)
2·38 (4·16)	0·273	1·78	2·18 (4·08)	0·220	1·90
2·28 (4·01)	0·225	1·73	2·25 (4·15)	0·290	1·90
				(g.-ions Me_3NH^+)	

The amine content is less, and the dinitrogen tetroxide content greater, than with the diethylammonium compounds, and the analysis of the reaction product is not altered significantly when trimethyl- is used in place of triethyl-ammonium nitrate. The total number of nitrate groups present (given in parentheses) indicate that the products are again based on the $[Zn(NO_3)_4]^{2-}$ ion, but the equilibrium (equation 1) is further displaced towards the right-hand side on substitution of the tertiary for the secondary amine.

Reaction with Tetraethylammonium Nitrate Solutions.—This reaction proceeded in a similar manner to those described above, and the product was again obtained as fine needles. The amine content of this product was very small (0·03 g.-ion/g.-atom of Zn). When heated, the product decomposed vigorously at 200°, emitting jets of blue flame.

THE UNIVERSITY, NOTTINGHAM. [*Received, September 2nd*, 1953.]

Crystalline 2 : 4-*Di*-O-*methyl*-D-*glucose*.

By D. J. BELL and D. J. MANNERS

[Reprint Order No. 4843.]

ALTHOUGH both methyl 2 : 4-di-*O*-methyl-α- and -β-D-glucopyranosides have been described (Robertson and Waters, *J.*, 1931, 1709; Reeves, Adams, and Goebel, *J. Amer. Chem. Soc.*, 1940, **62**, 2881; Dewar and Fort, *J.*, 1944, 492), the present authors are unaware of any report on the free sugar. This has now been obtained in crystalline form, together with certain crystalline derivatives, by a simple preparation starting from laminarin (essentially a β1 : 3-linked glucosan), as follows: Laminarin ⟶ *O*-trityl-laminarin ⟶ di-*O*-methyl-*O*-trityl-laminarin ⟶ crude di-*O*-methyl-D-glucose ⟶ methyl 2 : 4-di-*O*-methyl-β-D-glucoside ⟶ 2 : 4-di-*O*-methyl-D-glucose.

The new sugar is conveniently characterised through its crystalline triacetate or its aniline derivative. The constitution assigned depends on the following observations: (*a*) heated with phenylhydrazine at pH 4·5, the sugar yielded 4-*O*-methyl-D-glucosazone, (*b*) a solution of the sugar in dry methanol containing 2% of dry hydrogen chloride showed a constant $[\alpha]_D$ of +61·4°, after 72 hours, indicating failure to form a furanoside; (*c*) periodate oxidation of the sugar yielded 0·98 mole of formaldehyde; (*d*) the methyl β-pyranoside did not react with sodium metaperiodate within 260 hours; and (*e*) a mixed melting point of the sugar with 3 : 4-di-*O*-methyl-D-glucose was markedly depressed.

2 : 4-Di-*O*-methyl-D-glucose has been found in the hydrolysis products of the trimethyl ether of the dextran synthesised by *Betacoccus arabinosaceous* (Barker, Bourne, Bruce, and Stacey, *Chem. and Ind.*, 1952, 1156); it should be a useful reference compound in structural studies of glucosans containing 1 : 3- and 1 : 6-linkages.

Experimental.—Rotations were measured in 2-dm. tubes.

O-*Trityl-laminarin.* Dried laminarin (10·0 g.) was treated, in dry pyridine, with chlorotriphenylmethane under the conditions prescribed for cellulose by Honeyman (*J.*, 1947, 168). Use of less than 2·5 mols. of etherifying agent per expected primary alcoholic group gave poor yields. The mixture was poured into a large volume of methanol; the precipitated triphenylmethyl ether was collected and washed with methanol, dissolved in pyridine, filtered, and reprecipitated by methanol (yield, 23·6 g., 94%) (Found: CPh_3, 56·1. $C_{25}H_{24}O_5$ requires CPh_3, 60·1%).

Di-O-methyl-O-trityl-laminarin. Trityl-laminarin (25·0 g.), dissolved in dioxan (150 ml.), was stirred rapidly with methyl sulphate (60 ml.) and sodium hydroxide flakes (50 g.) at 50—60° for 6 hr. (Glen, Myers, and Grant, *J.*, 1951, 2568). Pouring the mixture into well-stirred ammonia solution (~ 1%) precipitated a pale yellow granular powder. A dioxan solution of the dried material was filtered through a well-packed layer of anhydrous sodium sulphate on a sintered-glass filter (porosity 3). The pale yellow filtrate was poured into water containing some sodium chloride (to assist flocculation), and the resulting precipitate of the ether dried under reduced pressure (over P_2O_5) (yield, 24·0 g., 90·0%) (Found: OMe, 14·6; CPh_3, 53·5. $C_{27}H_{28}O_5$ requires OMe, 14·3; CPh_3, 56·0%).

Methyl 2 : 4-di-O-methyl-β-D-glucoside. Dimethyltrityl-laminarin (24·0 g.) was stirred on the boiling-water bath with acetic acid (180 ml.), dioxan (100 ml.), and 2N-sulphuric acid (20 ml.), a clear yellow solution quickly resulting. A further 230 ml. of 2N-sulphuric acid was added in small portions to prevent formation of a precipitate. After 2 hr. the dioxan and acetic acid were removed by distillation under reduced pressure. The crystals of triphenylmethanol were filtered off and the filtrate was neutralised with barium carbonate. After filtration, and removal of traces of ions by Wadman's method (*J.*, 1952, 3051) the neutral fluid was evaporated under reduced pressure. The resulting syrup (4·0 g.) could not be crystallised (from it the 1 : 3 : 6-tri-*O*-acetate may be prepared, see below). The crude sugar (2·8 g.) was converted into the crystalline methyl β-glucoside (1·0 g.) by Oldham's procedure (*J. Amer. Chem. Soc.*, 1934, **56**, 1360); none of the intermediary products could be crystallised. Recrystallised twice from ether, the substance had m. p. 120—121° (Reeves *et al.*, *loc. cit.*, record m. p. 122—123°), $[\alpha]_D^{20}$ −26·8° (*c*, 3·4 in H_2O), −18·4° (*c*, 2·1 in acetone) {Dewar and Fort, *loc. cit.*, record $[\alpha]_D$ −16·3°, (*c*, 3·1 in acetone)}.

Periodate oxidation of methyl 2 : 4-di-O-methyl-β-D-glucoside. The substance (10·0 millimole) was treated (cf. Greville and Northcote, *J.*, 1952, 1945) with sodium metaperiodate (2·43 mols.). Periodate was not reduced in 260 hr.

2 : 4-Di-O-methyl-D-glucose. The glucoside (700 mg.) was hydrolysed with N-hydrochloric acid at *ca.* 100° to constant optical rotation (2 hr.). After neutralisation with silver carbonate, the filtered solution yielded a colourless syrup (600 mg.) which crystallised on drying in a high vacuum. Recrystallised from ethyl acetate or propyl acetate the *sugar* (fine needles) had m. p. varying from 125° to 129°, $[\alpha]_D^{20}$ +43·3° (4 min.) ⟶ +73·7° (const., 1000 min.) (*c*, 2·8 in H_2O) (Found: C, 46·2; H, 7·7; OMe, 29·6. $C_8H_{16}O_5$ requires C, 46·2; H, 7·7; OMe, 29·8%).

A 3·3% solution in dry methanol containing 2% (w/v) of hydrogen chloride had: $[\alpha]_D^{18}$ initial +76·7°; +72·5° (24 hr.); +65·5° (46 hr.); +61·4° (72 hr., const.) (cf. Irvine and Hirst, *J.*, 1922, **121**, 1213).

The sugar (46·0 mg.) was kept in a mixture of phosphate buffer (pH 7·5) and 6 ml. of 0·3M-sodium periodate for 36 hr. (cf. Bell and Greville, *J.*, 1950, 388), giving finally 63·4 mg. of formaldehyde–dimedone derivative, m. p. 191—193 (corr.) (0·98 mol.).

The sugar (69 mg.), heated at 100° for 6 hr. with 4·5 mols. of phenylhydrazine in 0·2M-sodium acetate buffer in the presence of bisulphite ion (Hamilton, *J. Amer. Chem. Soc.*, 1934, **56**, 487), yielded yellow needles of a monomethyl-phenylosazone. Recrystallised from 50% aqueous ethanol the substance (needles) melted at 158—160°, undepressed when mixed with the original sample of 4-*O*-methyl-phenyl-D-glucosazone of Munro and Percival (*J.*, 1935, 873) kindly provided by Dr. E. E. Percival (Found: N, 15·1; OMe, 9·6. Calc. for $C_{19}H_{24}O_4N_4$: N, 15·0; OMe, 8·4%).

2 : 4-Di-O-methyl-N-phenylglucosylamine. Treated with aniline (7 parts) in ethanol (10 parts) at 20° for 48 hr. (Dr. E. J. Bourne, personal communication), the sugar yielded an *aniline* derivative (fine needles from ethanol). Three preparations had m. p. 196° (Found: C, 59·2; H, 7·6; N, 5·6; OMe, 21·7. $C_{14}H_{21}O_5N$ requires C, 59·1; H, 7·4; N, 4·9; OMe, 21·9).

1 : 3 : 6-Tri-O-acetyl-2 : 4-di-O-methyl-β-D-glucose. With acetic anhydride and sodium acetate at 100° for 30 min., the sugar yielded the crystalline *1 : 3 : 6-tri-O-acetyl-2 : 4-di-O-methyl-β-D-glucose*, which crystallised from chloroform–light petroleum (b. p. 40—60°) as thick needles, m. p. 105—106°, $[\alpha]_D^{20}$ +11·5° (in $CHCl_3$; *c*, 7·3) (Found: C, 49·8; H, 6·6; OMe, 18·6. $C_{14}H_{22}O_9$ requires C, 50·3; H, 6·6; OMe, 18·6%).

The authors thank Dr. E. J. Bourne for information, Dr. E. T. Dewar for providing the laminarin, and Mr. G. Charalambous for some of the methoxyl determinations.

BIOCHEMISTRY DEPARTMENT, UNIVERSITY OF CAMBRIDGE.
CHEMISTRY DEPARTMENT, UNIVERSITY OF EDINBURGH. [*Received, November 28th*, 1953.]

Crystalline 1-O-*Methyl*-D-*fructose.*

By S. Bayne and Jennifer Wildy.

[Reprint Order No. 4860.]

Of the five possible monomethyl ethers of fructose only 3-*O*-methyl-D-fructose has been crystallised (Irvine and Hynd, *J.*, 1909, **95**, 1220). 1-*O*-Methyl-D-fructose was first obtained by Ohle (*Ber.*, 1925, **58**, 2577) by methylation of " β "-di-*O*-*iso*propylidene-D-fructose; the methods for its preparation and the evidence for the structure of the parent di-*O*-*iso*propylidenefructose have been reviewed recently by Barry and Honeyman (*Adv. Carbohydrate Chem.*, 1952, **7**, 81, 71).

1-*O*-Methyl-D-fructose has now been crystallised and obtained chromatographically pure. The crystalline sugar melts slowly at 76—78° when examined on the Kofler hot-stage microscope, and in methanol solution it exhibits well-marked mutarotation. Its constitution is confirmed by reconversion into 1-*O*-methyldi-*O*-*iso*propylidene-D-fructose on treatment with acid acetone, and by its reduction to crystalline 1-*O*-methyl-D-mannitol.

1-*O*-Methyl-D-fructose forms crystalline phenylhydrazones with phenylhydrazine and 2 : 5-dichlorophenylhydrazine. With an excess of phenylhydrazine, D-glucose phenylosazone is formed (cf. Ohle, *loc. cit.*). The displacement in this way of the methoxyl adjacent to the reducing group is now well established. Brigl and Schinle (*Ber.*, 1929, **62**, 1716) prepared glucosazone from 2-*O*-methyl-D-glucose and 6-*O*-methylglucosazone has been obtained from 2 : 6-di-*O*-methyl-D-glucose (Freudenberg and Hüll, *Ber.*, 1941, **74**, 237). Although Hibbert, Tipson, and Brauns (*Canad. J. Res.*, 1931, **4**, 235) were unable to prepare an osazone from 1 : 3 : 4-tri-*O*-methyl-D-fructose, Hirst, Mitchell, Percival, and Percival (*J.*, 1953, 3170) have recently obtained crystalline 4 : 5-di-*O*-methylglucosazone from 1 : 4 : 5-tri-*O*-methyl-D-fructose.

From its normal reducing properties and from its optical behaviour the crystalline sugar is probably β-1-*O*-methyl-D-fructopyranose.

Experimental.—M. p.s marked (*K*) were determined on a Kofler micro-melting-point block and these alone are corrected.

1-O-*Methyl*-2 : 3-4 : 5-*di*-O-iso*propylidene*-D-*fructose*. 2 : 3-4 : 5-Di-*O*-*iso*propylidene-D-fructose was methylated by the method of Glen, Myers, and Grant (*J.*, 1951, 2568). The syrupy product, after crystallisation from aqueous methanol and from light petroleum, had m. p. 48—49°, $[\alpha]_D^{20}$ −36·5° (*c*, 1·00 in EtOH).

1-O-*Methyl*-D-*fructose*. 1-*O*-Methyl-2 : 3-4 : 5-di-*O*-*iso*propylidene-D-fructose (9·0 g.) was heated at 100° for 6 hr. with 0·1N-sulphuric acid (200 c.c.), decolorised with charcoal, and neutralised with lead carbonate. After treatment with a mixture of ion-exchange resins (cf. Bell, *J.*, 1953, 1231) the solution was evaporated to a pale yellow syrup (6·3 g.) which crystallised. Recrystallisation from ethyl acetate–ethanol gave 1-O-*methyl*-D-*fructose*, m. p. 76—78° (*K*), $[\alpha]_D^{21}$ −110·9° ⟶ −52·7° (24 hr.; const.) (*c*, 1·822 in MeOH), −88·5° ⟶ −82·3° (20 min.; const.) (*c*, 2·26 in H_2O) (Found: C, 43·7; H, 7·3; OMe, 16·9. $C_7H_{14}O_6$ requires C, 43·3; H, 7·2; OMe, 16·0%).

On a paper chromatogram developed with *n*-butanol–acetic acid–water (4 : 1 : 5) and treated with triphenyltetrazole spray, 1-*O*-methyl-D-fructose had R_F 0·34 (3-*O*-methyl-D-fructose, R_F 0·36) and was free from fructose (R_F 0·21); it is less sweet than fructose and is very hygroscopic.

1-*O*-Methyl-D-fructose (1·0 g.) was dissolved in acetone containing 4% (w/v) sulphuric acid. After 12 hr. the di-*O*-*iso*propylidene derivative (0·6 g.), m. p. and mixed m. p. 48—49°, was isolated.

Phenylhydrazones and phenylosazones from 1-O-*methyl*-D-*fructose*. With phenylhydrazine, D-glucosephenylosazone, m. p. 207° (identified by conversion into 2-phenyl-4-D-*arabo*tetrahydroxybutyl-2 : 1 : 3-triazole, m. p. 194°), was obtained (cf. Brauns and Frush, *Bur. Stand. J. Res.*, 1931, **6**, 449). With 2 : 4-dinitrophenylhydrazine under the conditions described by Neuberg (*Arch. Biochem.*, 1946, **2**, 457) 1-*O*-methyl-D-fructose (116 mg.) gave D-glucose 2 : 4-dinitrophenylosazone (286 mg.). 1-O-*Methyl*-D-*fructose phenylhydrazone*, m. p. 133° (Found: C, 55·3; H, 7·3; N, 10·8. $C_{13}H_{20}O_5N_2$ requires C, 54·9; H, 7·0; N, 9·9%), and 1-O-*methyl*-D-*fructose*

2 : 5-*dichlorophenylhydrazone*, m. p. 139° (Found : C, 43·4; H, 5·0; N, 7·7. $C_{13}H_{18}O_5N_2Cl_2$ requires C, 44·2; H, 5·1; N, 7·9%), were prepared in the usual way.

Reduction of 1-O-*methyl*-D-*fructose*. 1-*O*-Methyl-D-fructose (1·47 g.) was refluxed for 2 hr. with freshly prepared Raney nickel (15 g.) in 70% ethanol (150 c.c.) (Karabinos and Ballum, *J. Amer. Chem. Soc.*, 1953, **75**, 4501). The filtrate was evaporated and the residue crystallised from methanol, giving 1-O-*methyl*-D-*mannitol* (0·4 g.), m. p. 119°, $[\alpha]_D^{20}$ +6·81° (*c*, 4·40 in H_2O) (Found : C, 42·9; H, 7·9; OMe, 18·0. $C_7H_{16}O_6$ requires C, 42·9; H, 8·2; OMe, 15·8%), identified by comparison with an authentic sample (Bayne, Fewster, and Hawksley, to be published) prepared from 5 : 6-anhydro-1 : 2-3 : 4-di-*O*-*iso*propylidene-D-mannitol (Wiggins, *J.*, 1946, 388).

DEPARTMENT OF BIOCHEMISTRY, UNITED COLLEGE,
ST. ANDREWS, FIFE.

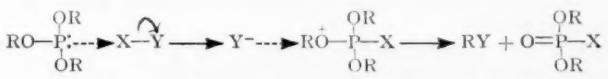
[*Received, December 3rd*, 1953.]

Some Phosphorus-containing Derivatives of 2 : 2 : 2-*Trichloroethanol.*

By W. GERRARD, W. J. GREEN, and R. J. PHILLIPS.

[Reprint Order No. 4759.]

ALCOHOLS readily react with phosphorus trichloride to form ultimately the trialkyl phosphite; from this, hydrogen chloride rapidly removes one alkyl group, and the second and the third such group if the alcoholic carbon atom is sufficiently reactive (Gerrard, *J.*, 1940, 1464; 1944, 85; Gerrard and Whitbread, *J.*, 1952, 914; Gerrard, Isaacs, Machell, Smith, and Wyvill, *J.*, 1953, 1920; Gerrard and Shepherd, *J.*, 1953, 2069). It has been suggested by Gerrard *et al.* (*J.*, 1952, 914) that interaction of an alkyl phosphite with hydrogen halide, halogen (Gerrard and Philip, *Research*, 1948, **1**, 477), or ethyl iodide (Arbusov, *J. Russ. Phys. Chem. Soc.*, 1906, **38**, 687; Kosolopoff, "Organophosphorus Compounds," Wiley, New York, 1950; Gerrard and Green, *J.*, 1951, 2550) involves a mechanism depicted thus :



where X = H, R, or Hal; Y = Hal. Chloretone and 2 : 2 : 2-trichloroethanol are the only alcohols yet shown not to conform with this scheme. The latter alcohol reacted comparatively slowly with phosphorus trichloride and gave the dichloridite, $PCl_2{\cdot}OR$, and chloridite, $PCl(OR)_2$, and also the trialkyl phosphite which is unique in that it can be isolated from the mixture, because it resists dealkylation by hydrogen chloride. With trichloro-*tert.*-butanol (chloretone) (Gerrard and Wyvill, *Research*, 1949, **2**, 536) reaction is even slower and goes no further than the chloridite, $PCl(OR)_2$, even in the presence of pyridine, a restriction attributed to steric hindrance to the properly oriented approach of the chloridite and the third molecule of alcohol.

Tris-2 : 2 : 2-trichloroethyl phosphite did not react with ethyl iodide; but it did readily with chlorine, and afforded the trialkyl phosphate by a mechanism still obscure. The usual reaction gives the phosphorochloridate : $P(OR)_3 + Cl_2 = RCl + P(O)Cl(OR)_2$. A plausible explanation for this departure from the above reaction scheme is that the nucleophilic reactivity of the lone pair of electrons on the phosphorus atom is reduced by the cumulative inductive effect of the 9 chlorine atoms, and in addition or alternatively, the function of the lone pair is hindered by the disposition of chlorine atoms in its vicinity. It could be suggested that the first step does occur, but that it is the "end-on" bimolecular replacement on carbon which is hindered by a disposition of groups similar to that prevailing in the *neo*pentyl structure (Dostrovsky, Hughes, and Ingold, *J.*, 1946, 173; Gerrard, Nechvatal, and Wilson, *J.*, 1950, 2088). In this case one would expect some evidence that the first step does occur, whereas in fact none was found.

The lone pair of electrons on the phosphorus atom in triphenyl phosphite can undergo reaction, although the second step is held up because the phenyl group is not usually amenable to nucleophilic substitution. However, there is no doubt that the first step in the overall reaction scheme has occurred; *e.g.*, the phosphite and methyl iodide afford triphenyl methyliodophosphoranetrioate, $(PhO)_3PMeI$, as a crystalline compound (Michaelis and Kähne, *Ber.*, 1898, **31**, 1048; Landauer and Rydon, *J.*, 1953, 2224).

2 : 2 : 2-Trichloroethanol reacted negligibly with phosphorus oxychloride alone; but in the presence of pyridine the dichloridate, $RO{\cdot}P(O)Cl_2$, was quickly formed, the chloridate was formed more slowly, and 5 days were required for nearly quantitative formation of the phosphate. The phosphite, however, was quickly formed when phosphorus trichloride was used in conjunction with pyridine.

Experimental.—Easily hydrolysable chlorine is denoted by Cl (e.h.). 2 : 2 : 2-Trichloroethanol was prepared by reduction of chloral (*Org. Synth.*, **15**, 80).

Interaction with phosphorus trichloride. By a general procedure (cf. Gerrard, *loc. cit.*) addition of the alcohol (4·5 g., 1 mol.) to phosphorus trichloride (6·2 g., 1·5 mols.) afforded 2 : 2 : 2-*trichloroethyl phosphorodichloridite* (2·2 g.), b. p. 42°/0·1 mm., n_D^{23} 1·5140 [Found: Cl (e.h.), 28·2. $C_2H_2OCl_5P$ requires Cl (e.h.), 28·3%], *bis*-(2 : 2 : 2-*trichloroethyl*) *phosphorochloridite* (1·22 g.), b. p. 95—96°/0·1 mm., n_D^{22} 1·5167 [Found: Cl (e.h.), 9·7. $C_4H_4O_2Cl_7P$ requires Cl (e.h.), 9·7%], tris-2 : 2 : 2-trichloroethyl phosphite (1·83 g.), b. p. 125—127°/0·1 mm., n_D^{23} 1·5178 (Found: Cl, 66·5. Calc. for $C_6H_6O_3Cl_9P$: Cl, 67·0%), and a residue (0·52 g.). The relative amounts of these compounds depend on the proportions of alcohol and trichloride, and on subsequent treatment. Even with 2 mols. of trichloride to 1 mol. of alcohol (8·1 g.), the reaction mixture, after being heated at 60—65° for 1 hr., gave the triester (4·0 g.), b. p. 133—135°/0·2 mm., n_D^{21} 1·5172 (Found: Cl, 66·8%), as well as the chloridite (2·9 g.), b. p. 95—96°/0·1 mm., n_D^{18} 1·5170 [Found: Cl (e.h.), 9·7%], and dichloridite (1·6 g.) [Found: Cl (e.h.), 28·3%]. The alcohol (8·14 g., 3 mols.) and trichloride (1 mol.), shaken mechanically for 6 hr. at 15°, afforded hydrogen chloride (which was absorbed by potassium hydroxide), unchanged alcohol (0·5 g.), and the triester, b. p. 129—130°/0·1 mm., n_D^{23} 1·5177 (Found: Cl, 67·0%); the yield of the ester (88%) corresponded closely with the amount of hydrogen chloride. The triester (84% yield), b. p. 122°/0·05 mm. (Found: Cl, 66·9%), was also obtained by addition of phosphorus trichloride (1 mol.) to the alcohol (3 mols.) and pyridine (3 mols.) in pentane at −10°, base hydrochloride (99·5%) (Found: Cl, 30·3; C_5H_5N, 67·7. Calc. for C_5H_5N,HCl: Cl, 30·7; C_5H_5N, 68·5%) being quickly obtained.

Treated with hydrogen chloride for 10 hr. at 95—100°, the triester, b. p. 128°/0·1 mm., n_D^{18} 1·5172 (Found: Cl, 66·5%), was recovered. The result was the same when hydrogen bromide was used.

The phosphite and ethyl iodide. After being heated with ethyl iodide at 95—105° for 18 hr., the phosphite (94%), b. p. 128°/0·1 mm., n_D^{22} 1·5175 (Found: Cl, 67·0%), was recovered.

The phosphite and chlorine. Passage (1 hr. at −15°) of dry chlorine into the phosphite (5·58 g.) dissolved in pentane caused immediate precipitation of white *tris*-2 : 2 : 2-*trichloroethyl phosphate* (4·32 g.), b. p. 160°/0·2 mm., m. p. 71—72° (Found: Cl, 64·8. $C_6H_6O_4Cl_9P$ requires Cl, 64·9%). The other products have not yet been identified.

The alcohol and phosphorus oxychloride. The phosphate (recryst. from pentane), m. p. 72° (Found: C, 14·4; H, 1·5; Cl, 64·8. Calc. for $C_6H_6O_4Cl_9P$: C, 14·6; H, 1·5; Cl, 64·9%), was obtained by addition of phosphorus oxychloride (1 mol.) to the alcohol (3 mols.) and pyridine (3 mols.) in ether at −10°. Complete precipitation of the base hydrochloride (97·6%) (Found: Cl, 29·4; C_5H_5N, 66·2%) required 5 days at 15°. In the absence of base, interaction of the alcohol (7·6 g.) and oxychloride (7·7 g.) was very slow. After being for 30 min. at 130°, the mixture showed no sign of reaction, and even after 160 hr. at 25°, a mere trace of hydrogen chloride was evolved, and evaporation at 25°/0·1 mm. left only 0·2 g. of residue.

Addition of pyridine (3·8 g., 1 mol.) to a mixture of alcohol (1 mol.) and oxychloride (1 mol.) in ether at −10° immediately precipitated the base hydrochloride, and the filtered solution afforded a residue (9·6 g., 20°/0·1 mm.) from which the *alkyl phosphorodichloridate* (5·7 g.), b. p. 57·5°/0·1 mm. [Found: Cl (e.h.), 26·5; Cl (total), 65·3. $C_2H_2O_2Cl_3P$ requires Cl (e.h.), 26·6; Cl (total), 66·6%], higher-boiling fractions (1·65 g.) containing decreasing amounts of easily hydrolysed chlorine, and a residue (1·6 g.) were obtained.

Action of heat on the phosphite. Kabachnik and Rossüskaya (*Bull. Acad. Sci. U.R.S.S.*,

Classe Sci. Chim., 1946, 403) have shown that tri-2-chloroethyl phosphite isomerises (40%) (cf. Arbusov, *loc. cit.*) when heated for 5 hr. at 150—160° :

$$(Cl{\cdot}CH_2{\cdot}CH_2{\cdot}O)_3P \longrightarrow Cl{\cdot}CH_2{\cdot}CH_2{\cdot}P(:O)(O{\cdot}CH_2{\cdot}CH_2Cl)_2$$

However, we found that when the 2 : 2 : 2-trichloroethyl ester (6·90 g.) was heated at 160—165° for 5 hr., it was recovered (6·15 g.), b. p. 134—135°/0·2 mm., n_D^{20} 1·5173 (Found : Cl, 67·0%).

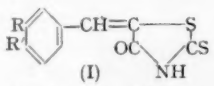
THE NORTHERN POLYTECHNIC, HOLLOWAY ROAD, N.7. [*Received, October 29th,* 1953.]

The Preparation of β-p-*Hydroxyphenyl-*α*-mercaptopropionic Acid and Some Related Acids, and the Action of Tyrosinase on the Former.*

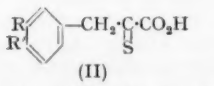
By D. G. BEW and G. R. CLEMO.

[Reprint Order No. 4829]

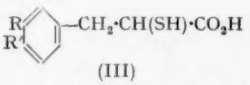
β-*p*-HYDROXYPHENYL-α-THIOPROPIONIC (II*a*) and some related acids have been prepared by the condensation of the corresponding aldehyde with rhodanine, followed by hydrolysis. Reduction in aqueous solution with sodium amalgam then gave the required mercapto-acids (III).



(I)



(II)



(III)

(*a* : R = H, R′ = OH.) (*b* : R = R′ = OH.) (*c* : R = H, R′ = OMe.) (*d* : R = R′ = OMe.)

The action of tyrosinase on β-*p*-hydroxyphenyl-α-mercaptopropionic acid (III*a*) was examined to see if hydroxylation to β-(3 : 4-dihydroxyphenyl)-α-mercaptopropionic acid (III*b*) and subsequent cyclisation to 5 : 6-dihydroxythionaphthen-2-carboxylic acid or 5 : 6-dihydroxythionaphthen would occur. It is possible that the action of the enzyme might cease with the production of (III*b*) since the functional group involved in the cyclisation has properties so widely different from those of the amino-group in tyrosine. The oxidation was carried out by drawing air through a buffered solution of the mercapto-acid (III*a*) in the presence of a solution of mushroom tyrosinase. A control experiment with tyrosine was carried out simultaneously to check the activity of the enzyme. Working up as described by Raper and Oxford (*Biochem. J.*, 1927, **21**, 89), which involved treatment with methyl sulphate, gave only β-*p*-methoxyphenyl-α-methylthiopropionic acid, identical with the product obtained by the action of methyl sulphate on an alkaline solution of (III*a*).

Unsuccessful attempts were also made to cyclise β-(3 : 4-dimethoxyphenyl)-α-mercapto-propionic acid to 5 : 6-dimethoxythionaphthen-2-carboxylic acid by the use of alkaline ferricyanide or bromine in chloroform.

Experimental.—Tyrosinase was prepared by the method of Mallette, Lewis, Ames, Nelson, and Dawson (*Arch. Bioch.*, 1948, **16**, 283).

β-*p*-Hydroxyphenyl-α-thiopropionic acid (II*a*) was prepared as described by Andreasch (*Monatsh.*, 1908, **39**, 435) and β-(3 : 4-dimethoxyphenyl)-α-thiopropionic acid (II*d*) by the procedure of Julian and Sturgis (*J. Amer. Chem. Soc.*, 1935, **57**, 1126).

β-p-*Hydroxyphenyl-*α*-mercaptopropionic acid* (III*a*). β-*p*-Hydroxyphenyl-α-thiopropionic acid (II*a*) (5 g.) was suspended in water (100 ml.) and shaken with excess of sodium amalgam (120 g. ; 4%) for 2 hr. on a water-bath. The solution was filtered, cooled in ice-salt, and acidified with hydrochloric acid. From the resultant gum the *acid* (III*a*) was obtained as a white solid by extraction with light petroleum (b. p. 60—80°). It recrystallised from water in small clusters (1·5 g., m. p. 120—123°) (Found : C, 54·3; H, 4·7. $C_9H_{11}O_3S$ requires C, 54·7; H, 5·1%).

3 : 4-*Dihydroxybenzylidenerhodanine.* Protocatechualdehyde (5 g.), rhodanine (5 g.), and sodium acetate (7·5 g.) were refluxed in glacial acetic acid (20 ml.) for ½ hr. Water (100 ml.)

was added and the mixture warmed on a water-bath for 10 min. The orange-red solid *product* was collected and crystallised from acetic acid [8·7 g.; m. p. 315—319° (decomp.)] (Found: C, 47·45; H, 2·8. $C_{10}H_7O_3NS_2$ requires C, 47·5; H, 2·8%).

β-(3 : 4-*Dihydroxyphenyl*)-α-*thiopropionic acid* (II*b*). The rhodanine (I*b*) (8·5 g.) was heated in 10% aqueous sodium hydroxide (70 ml.) on a water-bath for 15 min. The deep red-violet solution was cooled in a freezing mixture and acidified rapidly with 50% hydrochloric acid, and the bright yellow precipitate (7·1 g.) was collected, reprecipitated from solution in sodium carbonate, and crystallised from methanol. This *acid* had m. p. 281—285° (Found: C, 50·6; H, 3·6. $C_9H_8O_4S$ requires C, 50·9; H, 3·8%).

β-(3 : 4-*Dihydroxyphenyl*)-α-*mercaptopropionic acid* (III*b*). The thio-acid (II*b*) (5 g.), suspended in water (100 ml.), was stirred with sodium amalgam (130 g., 4%) for 2 hr. on a water-bath in an atmosphere of carbon dioxide. After filtration the solution was cooled in a freezing mixture and acidified with hydrochloric acid, and the resulting gum dissolved in chloroform, treated with animal charcoal, and concentrated, the *acid* being obtained as a cream-coloured solid (1·1 g.), m. p. 166—170° (Found: C, 50·7; H, 5·2. $C_9H_{10}O_4S$ requires C, 50·5; H, 4·7%).

p-*Methoxybenzylidenerhodanine and* β-p-*methoxyphenyl*-α-*thiopropionic acid* (cf. Andreasch and Zipser, *Monatsh.*, 1893, **24**, 515). *p*-Anisaldehyde (5 g.), rhodanine (5·5 g.), and sodium acetate (7·5 g.) in glacial acetic acid (20 ml.) were condensed and the product worked up as described for (I*b*), giving orange-red plates (7·4 g.), m. p. 230—234°. The rhodanine (I*c*) (7·2 g.) was hydrolysed as described for (II*b*), and the yellow solid obtained on acidification crystallised from methanol (5·8 g.; m. p. 166—169°).

α-*Mercapto*-β-p-*methoxyphenylpropionic acid* (III*c*). Reduction of the thio-acid (II*c*) (5 g.) with excess of sodium amalgam gave, on acidification, an *acid* (4·6 g.) which crystallised from water in rhombic crystals, m. p. 86—89° (Found: C, 56·9; H, 6·0. $C_{10}H_{12}O_3S$ requires C, 56·65; H, 5·7%).

β-(3 : 4-*Dimethoxyphenyl*)-α-*mercaptopropionic acid* (III*d*) was prepared from β-(3 : 4-dimethoxyphenyl)-α-thiopyruvic acid (II*d*) (5 g.) as described above and crystallised from water in monohydrated prisms (2·3 g.), m. p. 76—78° (Found: C, 50·8; H, 6·1; S, 11·8. $C_{11}H_{14}O_4S,H_2O$ requires C, 50·5; H, 6·2; S, 12·3%).

Oxidation procedure. A slow stream of filtered air was drawn through the mercapto-acid (III*a*) (0·2 g.), distilled water (30 ml.), buffer solution (pH 8; 10 ml.), and tyrosinase solution (4 ml.) for 50 hr. in a thermostat at 20°. The resulting red-brown solution was acidified with acetic acid, filtered, concentrated in a vacuum under nitrogen, saturated with sulphur dioxide, and set aside for 5 hr. before being neutralised with 20% aqueous sodium hydroxide. Further sodium hydroxide solution (10 ml.) was added, followed by methyl sulphate (4 ml.), the resulting solution was refluxed for ½ hr. and then cooled, and a small amount of a dark brown oil was extracted with ether. The solution was acidified and again extracted with ether, on removal of which and distillation β-p-*methoxyphenyl*-α-*methylthiopropionic acid* was obtained as a colourless oil (b. p. 145—147°/0·1 mm.) which crystallised (0·14 g.; m. p. 76—80°) (Found: C, 58·2; H, 5·9. $C_{11}H_{14}O_3S$ requires C, 58·5; H, 6·2%).

β-*p*-Hydroxyphenyl-α-mercaptopropionic acid (III*a*) (1·0 g.) in sodium hydroxide (25 ml.; 10%) was cooled in ice, and methyl sulphate (3 ml.) was added slowly. The solution was heated on a water-bath for ½ hr., cooled, acidified to Congo-red with hydrochloric acid, and extracted with ether. On removal of the solvent a pale yellow oil (b. p. 150—152°/0·2 mm.) was obtained which solidified on cooling (0·8 g.); this had m. p. 77—81°, not depressed by material prepared as in the previous paragraph (Found: C, 58·3; H, 6·0%).

One of us (D. G. B.) thanks the Department of Scientific and Industrial Research for a maintenance grant.

KING'S COLLEGE, NEWCASTLE-ON-TYNE. [*Received, November 24th*, 1953.]

A Statistical Study of Some Olefinic Absorption Bands in the Infra-red Region.

By R. L. Werner and P. D. Lark.

[Reprint Order No. 4689.]

In infra-red measurements of some compounds in which *iso*propylidene–*iso*propenyl isomerism was possible, there appeared to be an inverse relation between the C=C stretching frequency of the *iso*propylidene groups (range 1656—1680 cm.$^{-1}$) and the corresponding out-of-plane hydrogen bending frequency (range 812—858 cm.$^{-1}$). Data were collected to investigate this point and a statistical analysis was carried out on values from 31 compounds having the group $R^1R^2C{:}CR_3H$. This was extended to include a skeletal vibration frequency (range 789—810 cm.$^{-1}$) which appeared when the group in question formed part of a *cyclo*hexenyl ring (cf. Bladon, Fabian, Henbest, Koch, and Wood, *J.*, 1951, 2402).

This analysis revealed highly significant correlations between the bands and yielded two sets of regression equations of possible value in structural investigations. If X is the C–H bending frequency in cm.$^{-1}$, and Y the C=C stretching frequency in cm.$^{-1}$, then *

$$X' = 2735{\cdot}0 - 1{\cdot}1401Y \ldots\ldots (1);\ \text{s(e)} = 6{\cdot}49\ \text{cm.}^{-1}$$

[probable (50%) limits of estimate = $\pm 4{\cdot}5$ cm.$^{-1}$; 90% limits = $\pm 11{\cdot}1$ cm.$^{-1}$]

$$Y' = 2033{\cdot}4 - 0{\cdot}4373X \ldots\ldots (2);\ \text{s(e)} = 4{\cdot}02\ \text{cm.}^{-1}$$

[probable (50%) limits of estimate = $\pm 2{\cdot}8$ cm.$^{-1}$; 90% limits = $\pm 6{\cdot}8$ cm.$^{-1}$]

where s(e) is the standard error of estimate based on 29 degrees of freedom. The correlation coefficient between X and Y is $-0{\cdot}706$ which is highly significant, the probability of such a value arising by chance, were there no relation between X and Y, being less than one in 1000 ($P < 0{\cdot}001$). The confidence limits of prediction are rather wide, and it is obvious from them and from the correlation coefficient that factors other than experimental error of measurement have not been allowed for.

For the nine *cyclo*hexenes examined, where the analysis included a skeletal frequency (Z, cm.$^{-1}$) the following were obtained :

$r_{XY} = -0{\cdot}827$ (highly significant, $P < 0{\cdot}01$)	$r_{XY,Z} = -0{\cdot}923$ (highly significant, $P \sim 0{\cdot}001$)
$r_{XZ} = +0{\cdot}627$ (just significant, $P > 0{\cdot}1$)	$r_{XZ,Y} = +0{\cdot}846$ (highly significant, $P < 0{\cdot}01$)
$r_{YZ} = -0{\cdot}194$ (not significant)	$r_{YZ,X} = +0{\cdot}741$ (significant, $P < 0{\cdot}05$)

$X' = 1874{\cdot}6 - 1{\cdot}1252Y + 1{\cdot}0340Z \ldots (3)$; s(e) = 4·85 cm.$^{-1}$ (probable limits of estimate = $\pm 3{\cdot}5$ cm.$^{-1}$; 90% limits = $\pm 9{\cdot}4$ cm.$^{-1}$).

$Y' = 1711{\cdot}2 - 0{\cdot}7306X + 0{\cdot}7094Z \ldots (4)$; s(e) = 3·65 cm.$^{-1}$ (probable limits of estimate = $\pm 2{\cdot}6$ cm.$^{-1}$; 90% limits = $\pm 7{\cdot}1$ cm.$^{-1}$).

$Z' = 1019{\cdot}2 + 0{\cdot}6853X + 0{\cdot}7468Y \ldots (5)$; s(e) = 3·74 cm.$^{-1}$ (probable limits of estimate = $\pm 2{\cdot}7$ cm.$^{-1}$; 90% limits = $\pm 7{\cdot}2$ cm.$^{-1}$).

The X and Y values of the *cyclo*hexenes do not differ from the remainder in range or correlation, but analysis of variance of regression indicates that the improvement in correlation and in the equations, owing to allowance being made for the third variable, cannot be regarded as accidental ($P < 0{\cdot}05$). If, as we believe, the experimental errors

* For description of statistical analysis, see Lyle, " Regression Analysis, etc.," Oliver and Boyd Ltd., Edinburgh, 2nd edn., 1946. In this work accurate equations, allowing for distance from the centre of observed values, are given for computing the confidence limits of prediction.

(standard deviations) are of the order of 3 cm.$^{-1}$ in Y and 2 cm.$^{-1}$ in X and Z, the confidence limits of prediction of (3), (4), and (5) could not be greatly improved. The implication is that, whatever the functional relations may be, the three band frequencies are closely connected in a more or less linear way.

As there was no reason to consider any one band as dependent on the other one or two, all regression equations were computed and, for simplicity, all frequencies were regarded as being of equal weight. In the few cases where two or three experimental values of a C=C stretching frequency were available, these were averaged, and the means regarded as single observations. The analysis did not include data from the few compounds which have the double bond in a *cyclo*pentenyl ring. In these the stretching frequency is much depressed by strain, and the regression equations do not apply to them. The confidence limits quoted are a little low if band frequencies are well away from the middle of the range of values given above, on which the equations are based (see Lyle, *op. cit.*, p. 63).

To the authors' knowledge the methods of correlation and regression analysis have been little applied to spectral data of this type. Here, they have served to indicate the close connection of some absorption bands and have provided empirical equations which might be of use for diagnostic purposes. As an example of their use, consider the compound described as 24-hydroxychol-9(11)-ene, investigated by Bladon *et al.* (*loc. cit.*) and found to have a C–H bending frequency of 827 cm.$^{-1}$. From (2) we deduce that the C=C stretching frequency should be 1671·8 ± 6·8, say between 1665 and 1679 cm.$^{-1}$ with 90% confidence. Since the value given is 1644 cm.$^{-1}$, we conclude that it is highly exceptional, or the value is incorrect, or the compound has not the supposed structure. Its values were originally included in the analysis and rejected on adequate statistical grounds. Furthermore, unlike the other *cyclo*hexenyl compounds, it has no skeletal band.

N.S.W. University of Technology,
Sydney, Australia.

[*Received, October 1st*, 1953.]

---

*A Novel Method of Cyanoethylation. Part II.** 10-2′-*Cyanoethyl*-9 : 10-*dihydrophenanthridine.*

By R. J. Bates and J. Cymerman-Craig.

[Reprint Order No. 4717.]

Attempts to cyanoethylate 9 : 10-dihydrophenanthridine with vinyl cyanide resulted only in dehydrogenation to phenanthridine (Smith and Yu, *J. Amer. Chem. Soc.*, 1952, **74**, 1096) which was also the sole product of reaction with 1-bromo-3-chloropropane. Use of the amine-exchange method of cyanoethylation (Bauer, Cymerman, and Sheldon, *J.*, 1951, 3311) was therefore examined.

Phenanthridine readily gave a stable benzenesulphonate and picrate. The corresponding salts of 9 : 10-dihydrophenanthridine were, however, surprisingly unstable, reverting to phenanthridines on recrystallisation. The recrystallised product described by Ritchie (*J. Proc. Roy. Soc. N.S.W.*, 1945, **78**, 177) as 9 : 10-dihydrophenanthridine picrate may thus have been phenanthridine picrate. The constitution of 9 : 10-dihydrophenanthridine benzenesulphonate was proved by its conversion into the known 10-acetyl-9 : 10-dihydrophenanthridine.

Reaction of 9 : 10-dihydrophenanthridine benzenesulphonate and 2-diethylaminoethyl cyanide in commercial nitrogen (containing *ca.* 1% of oxygen) gave 10-2′-cyanoethylphenanthridone, also prepared in quantitative yield by direct cyanoethylation of phenanthridone. In pure nitrogen 10-2′-cyanoethyl-9 : 10-dihydrophenanthridine was obtained. This compound proved unstable on repeated recrystallisation; heating it with acetic anhydride resulted in a 50% conversion into phenanthridine.

* *J.*, 1951, 3311 is regarded as Part I.

9-Methylphenanthridine, like phenanthridine, gave stable salts, and was reduced by lithium aluminium hydride to the known 9 : 10-dihydro-compound whose salts were oxidised on recrystallisation, and it seems possible that the recrystallised 9 : 10-dihydro-9-methylphenanthridine picrate reported by Ritchie (*loc. cit.*) was a mixture with 9-methylphenanthridine picrate. The constitution of the benzenesulphonate of (IV) was proved by conversion into the known acetyl derivative. No cyanoethylation product was obtained from 9 : 10-dihydro-9-methylphenanthridine benzenesulphonate and 2-diethylaminoethyl cyanide, presumably because of the steric hindrance offered to the amino-group by the *ortho*-methyl group; it has been shown that such steric hindrance is an important factor in determining the yield of cyanoethylated product from aromatic amines, both by the amine-exchange reaction (unpublished observations) and direct cyanoethylation (Braunholtz and Mann, *J.*, 1953, 1817).

Experimental.—Phenanthridine. The *benzenesulphonate* crystallised from *iso*propanol as yellow needles, m. p. 218·5—219·5° (Found : N, 4·45. $C_{13}H_9N,C_6H_6O_3S$ requires N, 4·15%), and the picrate formed yellow needles, m. p. 238—240°, from 2-ethoxyethanol (Found : N, 13·5. Calc. for $C_{13}H_9N,C_6H_3O_7N_3$: N, 13·75%). Pictet and Ankersmit (*Ber.*, 1889, **22**, 3339) give m. p. >220° for the picrate, but do not give analytical results.

9 : 10-*Dihydrophenanthridine.* The *benzenesulphonate*, prepared by mixing methanolic solutions of the base (Wooten and McKee, *J. Amer. Chem. Soc.*, 1949, **71**, 2946) and benzenesulphonic acid, formed creamy-white microcrystals, m. p. 178—182°. The product was dried *in vacuo* at room temperature (Found: C, 64·85, 65·05; H, 5·8, 5·75. $C_{13}H_{11}N,C_6H_6O_3S,CH_3{\cdot}OH$ requires C, 64·9; H, 5·65%). Recrystallisation from *iso*propanol gave yellow needles, m. p. 215—216° undepressed on admixture with phenanthridine benzenesulphonate.

A cold methanolic solution of freshly-prepared 9 : 10-dihydrophenanthridine benzenesulphonate and potassium hydroxide was diluted with water (10 volumes) and extracted with ether. The residue from evaporation of the dried (Na_2SO_4) extracts was treated with acetic anhydride, and the mixture poured into ice–water. Crystallisation from aqueous alcohol gave 10-acetyl-9 : 10-dihydrophenanthridine, m. p. 107—108° (Ritchie, *loc. cit.*, gives m. p. 108°).

9 : 10-*Dihydrophenanthridine picrate* was obtained, by mixing cold solutions of the base and picric acid, as bright orange-red needles, m. p. 224—225° (Found : N, 13·75. Calc. for $C_{13}H_{11}N,C_6H_3O_7N_3$: N, 13·65%). The same picrate could also be obtained from 9 : 10-dihydrophenanthridine benzenesulphonate. Ritchie (*loc. cit.*) gives m. p. 238° for this compound. Recrystallisation gave yellow needles, identical (m. p. and mixed m. p.) with phenanthridine picrate, m. p. 238—240°.

10-2′-*Cyanoethylphenanthridone.* (*a*) 9 : 10-Dihydrophenanthridine benzenesulphonate (17 g., 0·05 mole), 2-diethylaminoethyl cyanide (8 g., 0·064 mole), and a few crystals of quinol were refluxed at 180° for 1 hr. in an atmosphere of dry nitrogen (technical). Treatment of the cold melt with acetone at 0° left a white solid (12·6 g.) which was fractionally crystallised from acetone, giving : (i) diethylammonium benzenesulphonate (8 g., 69%), m. p. and mixed m. p. 137°; (ii) 10-2′-*cyanoethylphenanthridone* (3 g., 26%), as needles, m. p. 169—170·5° from acetone (Found : C, 77·4; H, 5·35; N, 10·95. $C_{16}H_{12}ON_2$ requires C, 77·4; H, 4·85; N, 11·25%). The original acetone filtrate gave on distillation 2-diethylaminoethyl cyanide (2·2 g., 27·5%), b. p. 40—43°/1·2 mm., and extraction of the residue with light petroleum afforded a mixture of phenanthridine and dihydrophenanthridine (5·6 g., 62%).

(*b*) A solution of phenanthridone (2 g.) in pyridine (150 c.c.) was treated slowly in presence of a trace of benzyltrimethylammonium hydroxide with vinyl cyanide (5 c.c.) on the steam-bath. After 4 hr., pyridine (100 c.c.) was distilled off; the residual solution on cooling and dilution with water deposited 10-2′-cyanoethylphenanthridone (2·5 g., 98%) which crystallised as needles from chloroform–light petroleum (b. p. 60—90°), m. p. 170—170·5° undepressed on admixture with material prepared as in (*a*) (Found : N, 11·25%).

The *picrate* crystallised in yellow needles, m. p. 230—232° (decomp.), from 2-ethoxyethanol (Found : N, 14·3. $C_{16}H_{12}ON_2,C_6H_3O_7N_3$ requires N, 14·65%).

(*c*) A solution of phenanthridone (1 g.) in dimethylformamide (25 c.c.) was treated slowly with excess of vinyl cyanide in presence of a trace of potassium hydroxide, and heated (steam bath) for 5 min. 10-2′-Cyanoethylphenanthridone (1·24 g., 97%), m. p. 169·5—170°, was obtained.

10-2′-*Cyanoethyl*-9 : 10-*dihydrophenanthridine.* 9 : 10-Dihydrophenanthridine benzenesulphonate (19·7 g., 0·058 mole), 2-diethylaminoethyl cyanide (11·7 g., 0·09 mole), and a trace of quinol were refluxed at 180° for 1 hr. in an atmosphere of oxygen-free nitrogen. The cooled

melt was extracted with ice-cold acetone, and the residue was washed with hot water and crystallised from chloroform–light petroleum (b. p. 40—60°) giving *10-2'-cyanoethyl-9 : 10-dihydrophenanthridine* (2·7 g., 20%) as needles, m. p. 150—152° (Found : N, 12·05. $C_{16}H_{14}N_2$ requires N, 11·95%). The *benzenesulphonate* formed pale yellow needles, m. p. 213—214° (decomp.), from methanol (Found : N, 7·25. $C_{16}H_{14}N_2,C_6H_6O_3S$ requires N, 7·15%). A mixture with phenanthridine benzenesulphonate (m. p. 218·5—219·5°) had m. p. 191°.

Evaporation of the acetone extract and extraction of the residue with light petroleum (b. p. 40—60°) gave a mixture (3·4 g.) of phenanthridine and dihydrophenanthridine.

9-Methylphenanthridine. The *benzenesulphonate* formed needles (from water), m. p. 251·5—252·5° (Found : C, 68·15; H, 4·75; N, 3·65. $C_{14}H_{11}N,C_6H_6O_3S$ requires C, 68·35; H, 4·85; N, 4·0%); the *picrate* separated from 2-ethoxyethanol as yellow needles, m. p. 239·5° (decomp.) (Found : C, 57·4; H, 3·2; N, 12·85. $C_{14}H_{11}N,C_6H_3O_7N_3$ requires C, 56·9; H, 3·3; N, 13·25%).

9 : 10-Dihydro-9-methylphenanthridine. 9-Methylphenanthridine (17 g.) was introduced into a well-stirred ethereal solution of lithium aluminium hydride (1·6 g.) by a Soxhlet extractor during 10 hr. Addition of moist ether and 2N-hydrochloric acid, followed by basification of the separated hydrochloride and the aqueous layer, and extraction with ether, gave 9 : 10-dihydro-9-methylphenanthridine (10·4 g., 61%), prisms from light petroleum (b. p. 40—60°), m. p. 86—87° (Ritchie, *loc. cit.*, gives m. p. 89°). The *benzenesulphonate* had m. p. 205—207° (Found : N, 4·1. $C_{14}H_{13}N,C_6H_6O_3S$ requires N, 3·95%). After recrystallisation this m. p. rose to 250°, not depressed on admixture with 9-methylphenanthridine benzenesulphonate. 9 : 10-Dihydro-9-methylphenanthridine benzenesulphonate was converted into 10-acetyl-9 : 10-dihydro-9-methylphenanthridine, m. p. 100—101° undepressed on admixture with an authentic specimen (Ritchie, *loc. cit.*, gives m. p. 102°). Prepared from the base or from 9 : 10-dihydro-9-methylphenanthridine benzenesulphonate, the picrate formed red needles, m. p. 232° (decomp.) (Found : C, 56·6; H, 3·6; N, 13·0. Calc. for $C_{14}H_{13}N,C_6H_3O_7N_3$: C, 56·6; H, 3·75; N, 13·2%). Ritchie (*loc. cit.*) reports m. p. 220—240° (decomp.). On recrystallisation the compound was converted into 9-methylphenanthridine picrate, m. p. and mixed m. p. 239·5° (decomp.).

We are indebted to the late Mrs. E. Bielski for microanalyses.

UNIVERSITY OF SYDNEY, AUSTRALIA. [*Received, October 12th*, 1953.]

Preparation of Pentachlorothiophenol and Some Other Sulphur Compounds.

By WADIE TADROS and EZZAT SAAD.

[Reprint Order No. 4722.]

PENTACHLOROTHIOPHENOL and some other sulphur compounds have been prepared and tested for molluscicidal activity against *Biomphalaria boissyi mansoni*. The results of these tests will be published by Dr. Donald O. Hoffman.

When injected subcutaneously in solution in sesame oil (5 mg. in 0·4 c.c.) into groups of 5 ovariectomised 22-g. mice, *as*-di-*p*-ethylthiophenylethylene (4 doses of 0·1 c.c. during 2 days), *as*-di-*p*-ethylsulphonylphenylethylene, and 1 : 1-di-*p*-ethylsulphonylphenyl-2-phenylethylene (doses, as above, but 1·25 mg. in 0·4 c.c.) failed to show œstrogenic activity.

Experimental.—Pentachlorothiophenol. A solution of pentachlorobenzenediazonium chloride (Willgerodt and Wilcke, *Ber.*, 1910, **43**, 2746) (pentachloroaniline, 5 g.; acetic acid, 150 c.c.; concentrated hydrochloric acid, 100 c.c.; sodium nitrite, 10 g.; at 5°) was added gradually to a solution of potassium ethyl xanthate (6 g.) and sodium carbonate (250 g.) in water (500 c.c.), the temperature being kept at 70° during the addition, with subsequent shaking for 15 min. and storage overnight. The residue was filtered off, washed successively with water, dilute hydrochloric acid, water, 3% aqueous sodium hydroxide, and water, and then hydrolysed by refluxing alcoholic sodium hydroxide (sodium hydroxide, 5 g.; water, 10 c.c.; alcohol, 150 c.c.) for 1 hr. Alcohol was distilled off and the residue, after being treated with water, was filtered off. The filtrate was acidified with dilute hydrochloric acid; the precipitated *phenol*, crystallised from

glacial acetic acid, was colourless and had m. p. 240° (yield, *ca.* 20—25%) (Found: C, 26·3; H, 0·7; Cl, 63·1; S, 11·5. C_6HCl_5S requires C, 25·5; H, 0·4: Cl, 62·8; S, 11·3%).

Pentachlorothioanisole was prepared from pentachlorothiophenol (0·2 g.), alcoholic sodium ethoxide (sodium, 0·04 g.; alcohol, 25 c.c.), and methyl iodide (1 g.) on the water-bath during 1 hr. It had m. p. 95—96° (from alcohol) (yield, quantitative) (Found: C, 28·8; H, 1·4; Cl, 59·6; S, 10·4. $C_7H_3Cl_5S$ requires C, 28·3; H, 1·0; Cl, 59·9; S, 10·8%).

Pentachlorothiophenetole, similarly prepared, had m. p. 42—44° (from alcohol) (yield, quantitative) (Found: S, 9·9. Calc. for $C_8H_5Cl_5S$: S, 10·3%). Pollak, Heimberg-Krauss, Katscher, and Lustig (*Monatsh.*, 1930, **55**, 358) do not give a m. p.

Bispentachlorophenyl disulphide. To a solution of pentachlorothiophenol (0·5 g.) in carbon tetrachloride (10 c.c.), phosphorus pentachloride (0·37 g.) was added and the mixture was heated on the water-bath for 10 min. and then left overnight. Carbon tetrachloride was removed and the residue was treated with water, filtered off, washed with a few c.c. of 3% aqueous sodium hydroxide and then water. The *disulphide* (0·45 g.), crystallised from acetic acid, had m. p. 229° (Found: Cl, 63·5; S, 11·4. $C_{12}Cl_{10}S_2$ requires Cl, 63·1; S, 11·4%).

4 : 4′-*Dimercaptobenzophenone* was prepared in the same way as pentachlorothiophenol (4 : 4′-diaminobenzophenone, 25 g.; 12·5% hydrochloric acid, 400 c.c.; ice, 100 g.; sodium nitrite, 25·8 g.; potassium ethyl xanthate, 50 g.; sodium carbonate, 150 g.; water, 300 c.c.). The residue was hydrolysed with alcoholic sodium hydroxide (27 g. of sodium hydroxide in 500 c.c. of alcohol). The solution was filtered and the alkaline filtrate was acidified with hydrochloric acid. The precipitate was redissolved in 5% aqueous sodium hydroxide and reprecipitated with hydrochloric acid, twice. The ketone thus obtained and crystallised from alcohol had m. p. 165° (yield, 15 g.) (Found: C, 62·9; H, 4·3; S, 25·3. $C_{13}H_{10}OS_2$ requires C, 63·4; H, 4·1; S, 26·0%).

4 : 4′-Diethylthiobenzophenone was prepared from the dithiol (30 g.), sodium ethoxide (from 5·75 g. of sodium) in alcohol (200 c.c.), and ethyl iodide (50 g.) or ethyl sulphate (40 g.) at the b. p. for 45 min. It formed pale greenish crystals (30 g.) (from alcohol), m. p. and mixed m. p. 116—118° (cf. Tadros, *J.*, 1949, 442) (Found: C, 67·4; H, 6·2; S, 21·1. Calc. for $C_{17}H_{18}OS_2$: C, 67·5; H, 6·0; S, 21·2%). The dimethyl derivative, similarly prepared, had m. p. and mixed m. p. 125° (cf. Tadros, *loc. cit.*).

4 : 4′-*Diethylsulphonylbenzophenone.* 30% Hydrogen peroxide (12 c.c.) was added dropwise at room temperature to a solution of 4 : 4′-diethylthiobenzophenone (7·55 g.) in glacial acetic acid (25 c.c.). The solution was then heated for 1 hr. on the water-bath. Acetic acid was removed in steam, and the *ketone* recrystallised from alcohol; it had m. p. 142—143° (yield, 8·33 g.) (Found: C, 55·7; H, 5·1; S, 17·4. $C_{17}H_{18}O_5S_2$ requires C, 55·7; H, 5·0; S, 17·5%).

1 : 1-*Di*-p-*ethylsulphonylphenylethanol.* To a Grignard reagent prepared from methyl iodide (22·4 g.), magnesium (3·4 g.), and ether (100 c.c.) was added 4 : 4′-diethylsulphonylbenzophenone (12·2 g.) suspended in benzene (50 c.c.) and after 5 hours' stirring, the mixture was left overnight and then decomposed with aqueous ammonium chloride. The ether–benzene and aqueous ammonium chloride layers were filtered and the residue was washed with water. On removal of solvents, a very small amount of the product was also obtained, and was added to the main residue. The *disulphone* (10 g.) had m. p. 192° (from alcohol) (Found: C, 56·3; H, 5·5; S, 17·3. $C_{18}H_{22}O_5S_2$ requires C, 56·5; H, 5·8; S, 16·8%). 1 : 1-*Di*-p-*ethylsulphonylphenyl*-2-*phenylethanol*, similarly prepared (benzyl chloride, 3·8 g.; magnesium, 0·75 g.; ether, 100 c.c.; 4 : 4′-diethylsulphonylbenzophenone, 5·5 g.; benzene, 50 c.c.) and crystallised from alcohol, had m. p. 200° (yield, 4·5 g.) (Found: C, 62·7; H, 5·8; S, 14·3. $C_{24}H_{26}O_5S_2$ requires C, 62·9; H, 5·7; S, 14·3%).

as-*Di*-p-*ethylthiophenylethylene* was obtained directly from the Grignard reaction (4 : 4′-diethylthiobenzophenone, 1 g.; methyl iodide, 2·4 g.; magnesium, 0·38 g.; ether, 50 c.c.). Crystallised from alcohol it had m. p. 118° (yield, 1 g.) (Found: C, 71·7; H, 7·0; S, 21·1. $C_{18}H_{20}S_2$ requires C, 72·0; H, 6·7; S, 21·3%). as-*Di*-p-*ethylsulphonylphenylethylene* was obtained by refluxing on the sand-bath a solution of the alcohol (3 g.) in acetic acid (30 c.c.) containing concentrated sulphuric acid (0·7 c.c.) for 2 hr. and had m. p. 117—118° (from alcohol) (yield, 2 g.) (Found: C, 59·2; H, 5·4; S, 18·0. $C_{18}H_{20}O_4S_2$ requires C, 59·3; H, 5·5; S, 17·6%). 1 : 1-*Di*-p-*ethylsulphonylphenyl*-2-*phenylethylene*, similarly prepared and crystallised, had m. p. 156° (Found: C, 65·4; H, 5·6; S, 14·5. $C_{24}H_{24}O_4S_2$ requires C, 65·4; H, 5·5; S, 14·6%).

CHEMISTRY DEPARTMENT, FACULTY OF SCIENCE,
CAIRO UNIVERSITY, EGYPT.

[*Received, September 14th*, 1953.]

2-Acetoacetyl-4-methylphenol as a Reagent for Primary Amines.

By J. B. Harborne and A. S. Weaving.

[Reprint Order No. 4783.]

It has been shown that primary aliphatic amines can be characterised by reaction at room temperature with ω-acetyl-*o*-hydroxyacetophenones to give crystalline *o*-β-alkylaminocrotonylphenols, which show an intense greenish-yellow fluorescence in ultra-violet light (Baker, Harborne, and Ollis, *J.*, 1952, 3215). Previously, only 2-acetoacetylphenol was used for this purpose, but we now suggest the use of the 4-methyl derivative, since it can be obtained more economically than the parent compound (comparative yields from phenol and *p*-cresol are 17 and 63% respectively). A number of amines (see Experimental section) have been characterised by reaction with 2-acetoacetyl-4-methylphenol, and this compound has also been used successfully in place of 2-acetoacetylphenol as a spraying reagent for the detection of primary aliphatic amines in paper chromatography.

The reaction of 2-acetoacetyl-4-methylphenol with other types of amine has been investigated in some detail. It does not react at room temperature with primary aromatic amines (aniline, 2-aminopyridine) or secondary amines (diethylamine), but when heated in ethanol with aniline it gives 2-β-anilinocrotonyl-4-methylphenol, but in a much lower yield than that stated by Wittig and Blumenthal (*Ber.*, 1927, **60**, 1085). When heated with diethylamine in ethanol, it undergoes, not condensation, but cyclisation to 2 : 6-dimethylchromone. On the other hand, 2-acetoacetyl-4-methylphenol reacts slowly at room temperature, or more rapidly on heating, with *o*-, *m*-, and *p*-phenylenediamine. The chief product from the first was the mono-condensation compound, but there was evidence that some of bis-condensation compound was formed. On paper chromatograms, the three phenylenediamines, after spraying with this reagent, appear as bright yellow spots, which can be readily distinguished from the corresponding spot, given by primary aliphatic amines.

The copper complexes which were prepared by Baker, Harborne, and Ollis (*J.*, 1952, 1294) from *o*-β-alkylaminocrotonylphenols and cupric acetate and contained the unusual ratio of one molecule of Schiff's base to each copper atom, were found to be too insoluble for molecular-weight determinations. By increasing the size of the *N*-alkyl group in the Schiff's bases, two copper derivatives have now been prepared which are sufficiently soluble in chloroform for the molecular weight to be determined by ebullioscopic methods. Determinations with the copper derivatives of 2-β-decylamino- and 2-β-dodecylaminocrotonyl-4-methylphenols show that these complexes are dimeric.

Experimental.—*2-Acetoacetylphenol and its 4-methyl derivative.* These two phenols were prepared by known methods (Chattaway, *J.*, 1931, 2495; Rosenmund and Schnurr, *Annalen*, 1928, **460**, 56; Wittig, Bangert, and Richter, *Annalen*, 1926, **446**, 169) and the best yields at each stage were: Phenol ⟶ phenyl acetate (88%) ⟶ *o*-hydroxyacetophenone (35%) ⟶ 2-acetoacetylphenol (53%); *p*-cresol ⟶ *p*-tolyl acetate (91%) ⟶ 2-hydroxy-5-methylacetophenone (88%) ⟶ 2-acetoacetyl-4-methylphenol (78%).

Reaction of 2-acetoacetyl-4-methylphenol with primary aliphatic amines. The general method described by Baker, Harborne, and Ollis (*J.*, 1952, 3215) was used. The products were crystallised from ethanol, with the exception of the ethylenediamine derivative, which was crystallised from benzene.

o-β-*Alkylaminocrotonyl-4-methylphenols.*

Amine	M. p.	Yield (%)	Formula	Found (%) C	H	N	Required (%) C	H	N
Ethyl-	125°	47	$C_{13}H_{17}O_2N$	71·1	7·5	6·6	71·2	7·7	6·4
n-Butyl-	86	54	$C_{15}H_{21}O_2N$	72·5	8·3	5·8	72·8	8·5	5·7
n-Hexyl-	81—82	63	$C_{17}H_{25}O_2N$	73·9	9·0	5·2	74·2	9·1	5·1
Benzyl-	123	66	$C_{18}H_{19}O_2N$	76·4	6·5	5·2	76·9	6·7	5·0
n-Octyl-	67	41	$C_{19}H_{29}O_2N$	—	—	4·6	—	—	4·6
n-Decyl-	62—63	79	$C_{21}H_{33}O_2N$	75·6	9·8	4·0	76·1	10·0	4·2
n-Dodecyl-	65—66	71	$C_{23}H_{37}O_2N$	76·7	10·2	4·1	76·3	10·3	3·9
Ethylenediamine-	236 (decomp.)	41	$C_{24}H_{28}O_4N_2$	70·3	6·7	6·7	70·6	6·9	6·9

Copper derivatives of 2-β-*decylamino- and* 2-β-*dodecylamino-crotonyl-4-methylphenol.* These *copper* derivatives were prepared by mixing ethanolic solutions of these compounds with ethanolic cupric acetate; they crystallised from benzene as green needles, m. p. 225° (decomp.) [Found: C, 63·9; H, 8·1; N, 3·8; Cu, 14·4%; *M* (ebullioscopic in chloroform), 763. $(C_{21}H_{31}O_2NCu)_2$ requires C, 64·2; H, 7·9; N, 3·6; Cu, 16·2%; *M*, 785], and m. p. 209—210° [Found: C, 65·4; H, 8·2; N, 3·4; Cu, 15·8%; *M* (ebullioscopic in chloroform), 779. $(C_{23}H_{35}O_2NCu)_2$ requires C, 65·6; H, 8·3; N, 3·3; Cu, 15·2%; *M*, 808], respectively.

The authors thank Professor W. Baker, F.R.S., for his interest in this work.

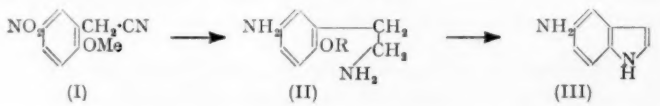
THE UNIVERSITY, BRISTOL.
[Present address of J. B. H.: DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, LOS ANGELES, CALIF., U.S.A.] [*Received, November 10th,* 1953.]

5-*Aminoindole.*

By JOHN HARLEY-MASON and A. H. JACKSON.

[Reprint Order No. 4805.]

OXIDATION of 2-(2 : 5-dihydroxyphenyl)ethylamine has been shown (Cromartie and Harley-Mason, *J.*, 1952, 2525) to give 5-hydroxyindole in high yield. It has now been found that oxidation of 2-(5-amino-2-hydroxyphenyl)ethylamine (II; R = H) gives 5-aminoindole (III), though in lower yield. Of the oxidising agents tried only silver oxide proved to be satisfactory.



(I) (II) (III)

Chloromethylation of *p*-nitroanisole (cf. Quelet, *Bull. Soc. chim.*, 1934, **5**, 539) gave 2-methoxy-5-nitrobenzyl chloride, which with potassium cyanide gave 2-methoxy-5-nitrobenzyl cyanide (I). Hydrogenation of (I) over palladium–charcoal gave 5-amino-2-methoxybenzyl cyanide, while with platinum oxide 2-(5-amino-2-methoxyphenyl)ethylamine (II; R = Me) was formed. Demethylation with hydrobromic acid gave (II; R = H), which was oxidised to the indole (III).

Experimental.—2-*Methoxy-5-nitrobenzyl chloride.* A mixture of *p*-nitroanisole (50 g.), paraformaldehyde (7·5 g.), finely powdered anhydrous zinc chloride (9 g.), and light petroleum (b. p. 100—120°; 75 c.c.) was stirred vigorously at 70° and saturated (10—15 min.) by a rapid stream of hydrogen chloride. After cooling, the mixture was added to ice-cold water (250 c.c.) and ethyl acetate (200 c.c.) with stirring. The organic layer was separated, washed with sodium carbonate solution, and dried ($MgSO_4$), and the solvent removed. On distillation of the residue, *p*-nitroanisole (15 g.), b. p. 85°/0·1 mm., was followed by 2-methoxy-5-nitrobenzyl chloride (22·5 g.), distilling at 120°/0·1 mm., which solidified (m. p. 75—77°) and was used directly for the next stage.

2-*Methoxy-5-nitrobenzyl cyanide.* The chloride (10 g.) and potassium cyanide (6 g.) in ethanol (45 c.c.) and water (15 c.c.) were refluxed for 2 hr. The resulting dark brown solution was poured into water (250 c.c.) and filtered from some tarry material, and the product extracted with ethyl acetate (3 × 150 c.c.). The dark reddish-brown extract was decolorised by passage through charcoal, and removal of the solvent then left the crude nitro-cyanide (7·9 g.). 2-*Methoxy-5-nitrobenzyl cyanide,* on recrystallisation from aqueous ethanol, formed prisms, m. p. 108—109° (Found: C, 56·3; H, 4·4. $C_9H_8O_3N_2$ requires C, 56·2; H, 4·2%).

Reduction of the nitro-cyanide. (*a*) The nitro-cyanide (1 g.) in ethanol (50 c.c.) and concentrated hydrochloric acid (1 c.c.) was hydrogenated over palladium–charcoal at room temperature and pressure. Absorption ceased when 3 mol. of hydrogen had been taken up:

the catalyst was then filtered off and the filtrate evaporated to dryness under reduced pressure at 40—50°. Recrystallised from ethanol–ether the residue gave *5-amino-2-methoxybenzyl cyanide hydrochloride* as fine white needles, m. p. 230—232° with previous darkening (Found : C, 54·3; H, 5·6. $C_9H_{11}ON_2Cl$ requires C, 54·4; H, 5·5%).

(*b*) The nitro-cyanide (2 g.), dissolved in ethanol (100 c.c.) and concentrated hydrochloric acid (2 c.c.), was hydrogenated over platinum oxide at 4—5 atm. at room temperature. After the catalyst had been filtered off, the solvent was removed under vacuum and the residual solid recrystallised from ethanol–ether, giving *2-(5-amino-2-methoxyphenyl)ethylamine dihydrochloride* as needles, m. p. 267—268° (decomp., with previous darkening) (Found : C, 44·9; H, 6·9. $C_9H_{16}ON_2Cl_2$ requires C, 45·2; H, 6·7%).

5-Aminoindole. The foregoing dihydrochloride (5 g.) was refluxed for 1 hr. with hydrobromic acid (*d* 1·49; 25 c.c.). The solution was diluted with water and evaporated to dryness under reduced pressure of hydrogen. A solution of the dark brown residue in water was boiled with charcoal and evaporated, and the residue recrystallised from ethanol–ether (charcoal), giving *2-(5-amino-2-hydroxyphenyl)ethylamine dihydrobromide* as small prisms, m. p. 247—248° (decomp.) (Found : C, 31·0; H, 4·5. $C_8H_{14}ON_2Br_2$ requires C, 31·6; H, 4·5%).

This dihydrobromide (0·82 g.) and sodium acetate (0·45 g.) were dissolved in water (100 c.c.), and the solution shaken vigorously with silver oxide (1 g.) for 5 min. An intense transient reddish-violet colour appeared at first, but this faded rapidly. The silver and unreacted silver oxide were filtered off and a little sodium dithionite added to the almost colourless filtrate before extracting it with ethyl acetate (3 × 100 c.c.). The dried ($MgSO_4$) extracts were evaporated under reduced pressure of hydrogen, and the residue sublimed at 60—80°/10^{-4} mm., yielding *5-aminoindole* (60—70 mg., 20—25%) as prisms, m. p. 125—127°. On recrystallisation from light petroleum (b. p. 100—120°) fine needles, m. p. 127—129°, were obtained (Found : C, 72·5; H, 6·0; N, 21·0. $C_8H_8N_2$ requires C, 72·7; H, 6·2; N, 21·2%). The ultra-violet absorption spectrum, measured in 95% ethanol ($\lambda_{max.}$ 2720, 3060 Å; $\varepsilon_{max.}$ 5700, 2950 : $\lambda_{min.}$ 2500, 2940 Å; $\varepsilon_{min.}$ 3050, 2600), was very similar to that of 5-hydroxyindole. With Ehrlich's reagent, a bright pink colour was given, while diazotisation followed by coupling with β-naphthol gave a deep brick-red precipitate.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, November 17th*, 1953.]

Synthesis of 2-Chloro-6-methylphenoxyacetic Acid.

By J. H. BARNES and P. G. MARSHALL.

[Reprint Order No. 4864.]

DURING a study of methods of assay, by ultra-violet spectroscopic photometry, of technical preparations of the selective herbicide 4-chloro-2-methylphenoxyacetic acid (cf. Grabe, *Acta Chem. Scand.*, 1950, **4**, 806; Hill, *Analyst*, 1952, **77**, 67), the need arose for a specimen of the isomeric 2-chloro-6-methylphenoxyacetic acid. The methods of preparation of the parent 2-chloro-6-methylphenol, described by Huston and Neeley (*J. Amer. Chem. Soc.*, 1935, **57**, 2176) and Sjöberg (*Acta Chem. Scand.*, 1950, **4**, 798) did not give material of sufficient purity. If, however, the intermediate 4-hydroxy-3-methylbenzenesulphonic acid, not isolated in Huston and Neeley's method, was purified through its aniline salt (Tatibouët and Setton, *Bull. Soc. chim.*, 1952, **19**, 382) before chlorination and desulphonation, the resulting 2-chloro-6-methylphenol readily gave pure 2-chloro-6-methylphenoxyacetic acid. A specimen of this phenol, which gave the pure phenoxyacetic acid, was also prepared from 2-methyl-6-nitrophenol (Monti, *Gazzetta*, 1937, **67**, 628), the toluene-*p*-sulphonate of which was reduced to the amine, then converted into 2-chloro-6-methylphenyl toluene-*p*-sulphonate and hydrolysed.

Experimental.—*2-Methyl-6-nitrophenyl toluene*-p-*sulphonate.* A solution of 2-methyl-6-nitrophenol (Monti, *loc. cit.*) (15·3 g., 1 mol.) and toluene-*p*-sulphonyl chloride (38 g., 2 mols.) in anhydrous pyridine, protected from moist air, was heated on the steam-bath for 1 hr., then

cooled and poured into water (600 ml.). The resulting gum gradually solidified and was washed with 2N-hydrochloric acid and with water, and recrystallised from ethanol, giving the *ester* (28·7 g., 94%) as prisms, m. p. 70—70·5° (Found: C, 54·4; H, 4·1; N, 4·8. $C_{14}H_{13}O_5NS$ requires C, 54·7; H, 4·3; N, 4·6%).

2-Amino-6-methylphenyl toluene-p-sulphonate. The above nitro-compound (19·3 g.) in glacial acetic acid (200 ml.) was hydrogenated, at a pressure of 45 atm., in the presence of palladised charcoal (10%; 3 g.) during 3 hr. The suspension was filtered in an atmosphere of carbon dioxide, and the filtrate evaporated to dryness under reduced pressure below 50°. Recrystallisation of the residue from aqueous ethanol gave prisms of the *amine* (14·4 g., 83%), m. p. 89—90° (Found: C, 60·0; H, 5·3; N, 5·35. $C_{14}H_{15}O_3NS$ requires C, 60·6; H, 5·45; N, 5·05%).

Sandmeyer reaction of 2-amino-6-methylphenyl toluene-p-sulphonate. The amine (20·8 g.; finely powdered), concentrated hydrochloric acid (25 ml.), and water (25 ml.) were vigorously stirred, with warming, giving a suspension of the difficulty soluble hydrochloride. To this, stirred at 0°, was added, gradually, sodium nitrite (7 g.) in water (50 ml.), to form a clear solution which was stirred at 0° for 2 hr. After addition of urea to destroy the excess of nitrous acid, the diazonium salt solution was added during 20 min. (chilled funnel) to a stirred solution of cuprous chloride (20 g.) in concentrated hydrochloric acid (50 ml.). The resulting mixture was stirred for a further hr., then extracted three times with ether. The combined extracts were washed with water and dried (Na_2SO_4) and the ether was removed, leaving a mixture (20 g.) of crystalline material and gum. Separation was effected by washing the mixture with ether, in which the gum was very soluble. The solid remaining was recrystallised from ethanol, to give long needles (5·5 g.) of an unidentified substance, m. p. 152—153° [Found: C, 63·9; H, 4·85; S, 13·2%; *M* (Rast), 224]. This material, which was insoluble in aqueous alkali, contained neither nitrogen nor chlorine. The gum was recovered by removal of ether and a portion was distilled; a first, small fraction, b. p. 118—158°/0·1 mm., and a second, main fraction, b. p. 158—168°/0·1 mm., were collected. Redistillation of the second fraction, through a Vigreux column, gave mainly material having b. p. 168°/0·1 mm.; this solidified when chilled and gave, by recrystallisation from ethanol, large prisms of *2-chloro-6-methylphenyl toluene-p-sulphonate*, m. p. 53—54° (Found: C, 57·0; H, 4·0; Cl, 12·05. $C_{14}H_{13}O_3SCl$ requires C, 56·65; H, 4·4; Cl, 11·95%).

2-Chloro-6-methylphenoxyacetic acid. The foregoing ester (1 g.) was heated with ethanol (10 ml.) and aqueous 2N-sodium hydroxide (20 ml.) under reflux. The mixture rapidly became homogeneous but heating was continued for 6 hr. An excess of 2N-hydrochloric acid was then added and the mixture was distilled with steam; the distillate contained 2-chloro-6-methylphenol, which was isolated with ether as an oil (0·46 g., 92%).

2-Chloro-6-methylphenol, obtained as above (0·66 g., 1 mol.), and ethyl bromoacetate (0·77 g., 1 mol.), were added, in a small volume of ethanol, to a solution from sodium (0·11 g., 1 equiv.) and ethanol (20 ml.), and the mixture was heated under reflux for 2 hr. After addition of 2N-sodium hydroxide (25 ml.) refluxing was continued for a further 90 min. The mixture was then acidified and extracted three times with ether; the combined extracts, washed with water and dried (Na_2SO_4), yielded on evaporation the acid, which crystallised from *cyclo*hexane as plates, m. p. 105—108·5° (0·45 g., 48%). Further recrystallisation, from benzene, furnished needles, m. p. 107·5—109° (Sjöberg gives m. p. 108·9—109·3°) (Found: C, 53·9; H, 4·2; Cl, 17·7. Calc. for $C_9H_9O_3Cl$: C, 53·9; H, 4·5; Cl, 17·7%). Light absorption in MeOH: max. at 267 mμ, log ε 2·51; inflexion at 273 mμ, log ε 2·44 (Grabe records a maximum at *ca.* 267 mμ).

2-Chloro-6-methylphenoxyacetic acid from 4-hydroxy-3-methylbenzenesulphonic acid. 4-Hydroxy-3-methylbenzenesulphonic acid, m. p. *ca.* 50°, prepared by sulphonation of *o*-cresol at 0—5° (Tatibouët and Setton, *loc. cit.*) (10·7 g.), in dry dioxan (20 ml.), was treated with a slow stream of chlorine, whereupon the temperature of the mixture rose to *ca.* 60°, with evolution of hydrogen chloride. After a few min., the mixture had increased in weight by 3 g. (theor., for 1 Cl, 2 g.). The dioxan was removed under reduced pressure and the dark residue, in ethereal solution, was extracted three times with water. The ethereal layer, after drying (Na_2SO_4) and evaporation, gave an oil (1·1 g.) which crystallised; the m. p., 50—55°, was undepressed on admixture with a sample of 2 : 4-dichloro-6-methylphenol, m. p. 54—55° (Zincke, *Annalen*, 1918, **417**, 206). Evaporation of the combined aqueous extracts, under reduced pressure, gave crude 3-chloro-4-hydroxy-5-methylbenzenesulphonic acid, m. p. 109—112°, decomp. *ca.* 140°. This product, on steam-distillation, gave a steam-volatile oil (0·80 g.), which was discarded, and subsequent distillation with superheated steam gave 2-chloro-6-methylphenol (2·28 g.). This was converted into 2-chloro-6-methylphenoxyacetic acid by the method previously employed. The product, recrystallised from *cyclo*hexane and from benzene, had m. p. 107—109°, un-

depressed on admixture with the acid obtained by the previous route; the yield was 1·2 g. (10·5% based on 4-hydroxy-3-methylbenzenesulphonic acid).

The authors thank Miss D. Hayward for assistance in the experimental work.

BRITISH SCHERING RESEARCH INSTITUTE,
BROOK LANE, ALDERLEY EDGE.

[*Received, December 5th*, 1953.]

---

2 : 6-*Bis*-2′-*hydroxyethylnaphthalene.*

By MORTON MEADOW and WILSON M. WHALEY.

[Reprint Order No. 4813.]

2 : 6-BIS-2′-HYDROXYETHYLNAPHTHALENE, desired as an intermediate for the synthesis of *iso*quinolino(8′ : 7′-7 : 8)*iso*quinoline, has been prepared in 21% overall yield from 2 : 6-dibromonaphthalene. The diol was prepared by the reaction of ethylene oxide with 2 : 6-naphthalenedilithium, the latter compound being formed by the halogen–metal interconversion reaction (Jones and Gilman *Org. Reactions*, 1951, **6**, 339) between 2 : 6-dibromonaphthalene and *n*-propyl- or *n*-butyl-lithium (Gilman, Beel, Brannan, Bullock, Dunn, and Miller, *J. Amer. Chem. Soc.*, 1949, **71**, 1499). 2 : 6-Dibromonaphthalene would not react with metallic lithium or magnesium in butyl ether or ethyl ether under various conditions. 2-Bromo-6-iodonaphthalene, prepared by a Sandmeyer reaction (Hodgson and Walker, *J.*, 1933, 1620) from 6-bromo-2-naphthylamine, also failed to react with metallic magnesium in ethyl ether, and was less effective in the halogen–metal interconversion than the dibromo-compound.

Unsuccessful attempts were made to prepare a di-Grignard reagent from 1 : 5-dibromonaphthalene (Lock, *Monatsh.*, 1950, **81**, 852; Fries and Köhler, *Ber.*, 1924, **57**, 500) although this reaction is claimed to proceed in excellent yield (Salkind, *Ber.*, 1934, **67**, 1031). Examination of the products obtained by treating the Grignard solutions with ethylene oxide indicated that one bromine atom was completely replaced and the second one to a limited extent.

Experimental.—M. p.s were determined with a calibrated apparatus. Microanalyses are by Galbraith Laboratories, Knoxville 17, Tennessee, U.S.A.

2 : 6-*Bis*-2′-*hydroxyethylnaphthalene.* 2 : 6-Dibromonaphthalene was prepared in 24% yield from 6-bromo-2-naphthylamine (Franzen and Stauble, *J. prakt. Chem.*, 1921—22, **103**, 352, 380, 387 *et seq.*) by a Sandmeyer reaction (Hodgson and Walker, *loc. cit.*). A solution of *n*-propyl-lithium (Gilman *et al.*, *loc. cit.*), prepared from distilled *n*-propyl bromide (15·8 g.) and lithium (2·19 g.) in di-*n*-butyl ether (70 c.c.) at −10° to 10°, was filtered into a dropping funnel and added during 5 min. to a solution of 2 : 6-dibromonaphthalene (4·5 g.) in benzene (50 c.c.) and *n*-butyl ether (100 c.c.). After 3 min. there was slowly added a cold solution of ethylene oxide (22 g.) in butyl ether (50 c.c.). After 10 min., the mixture was hydrolyzed with hydrochloric acid (100 c.c. of water and 100 c.c. of hydrochloric acid, *d* 1·18), and the organic phase was washed with water (4 × 200 c.c.) which precipitated a white solid in the aqueous phase. The collected solid, 2 : 6-*bis*-2′-*hydroxyethylnaphthalene* (0·7 g., 21%), formed shiny white plates, m. p. 147·5—148° [from 50% ethanol (charcoal)] (Found: C, 77·5; H, 7·5. $C_{14}H_{16}O_2$ requires C, 77·7; H, 7·5%). The compound was prepared in 19% yield by using *n*-butyl-lithium; in this case the product was isolated by distilling the organic layer *in vacuo*.

Attempts to prepare 2 : 6-bis-2′-aminoethylnaphthalene from 2 : 6-bis-2′-hydroxyethylnaphthalene through the corresponding dibromide were unsuccessful. Conversion of the diol into the dibromide by refluxing it with phosphorus tribromide in benzene (Kon and Ruzicka, *J.*, 1936, 189) yielded an impure product (m. p. 155·5—157°) which could not be converted into the diamine by treatment with aqueous ammonia in a Parr shaker for 4 days.

2-*Bromo*-6-*iodonaphthalene.* 6-Bromo-2-naphthylamine (111 g.) was diazotized by nitrosyl-

sulphuric acid (Hodgson and Walker, *loc. cit.*), and the diazonium solution slowly poured into a well-stirred solution of potassium iodide (249 g.) in water (500 c.c.). The mixture was stirred for 1 hr., set aside overnight, diluted with an equal volume of water, and filtered. The solid was dissolved in ethanol (8 l.), diluted with water (10 l.), and treated with sulphur dioxide. The solid, after recrystallization from ethanol by the Soxhlet-extractor method, was thoroughly washed with cold sulphuric acid (*d* 1·84) followed by ice-water, and dried. Sublimation at 200—210°/0·2 mm. followed by recrystallization from ethanol afforded pink leaflets (97 g., 57%) of 6-*bromo*-2-*iodonaphthalene*, m. p. 170—171° [Found: C, 35·9; H, 1·8; Br, 53·9. $C_{10}H_6BrI$ requires C, 36·1; H, 1·8; halogen (calc. as Br), 54·0%].

The authors of this and the following note are grateful for the financial support of the National Cancer Institute of The National Institutes of Health, Bethesda 14, Maryland, U.S.A.

THE UNIVERSITY OF TENNESSEE, KNOXVILLE 16, TENNESSEE, U.S.A.

[Present Addresses: (M. M.) NEW YORK UNIVERSITY, WASHINGTON SQUARE COLLEGE, NEW YORK 3. (W. M. W.) PABST LABORATORIES, MILWAUKEE 3, WISCONSIN.]

[*Received, November 19th*, 1953.]

Some Derivatives of Phenanthrene.

By MORTON MEADOW and WILSON M. WHALEY.

[Reprint Order No. 4814.]

THE selenium dioxide oxidation of 3-acetylphenanthrene (Mosettig and van de Kamp, *J. Amer. Chem. Soc.*, 1930, **52**, 3704) was found to yield 3-phenanthrylglyoxal. The glyoxal was apparently a hydrated acetal and was therefore characterized as the quinoxaline and dithiosemicarbazone.

2-Hydroxyiminoacetylphenanthrene was desired as an intermediate for the preparation of 7 : 8-α-naphth*iso*quinoline. Its preparation from 2-acetylphenanthrene with *n*-amyl nitrite in ethanolic sodium hydroxide has been described (van de Kamp, Burger, and Mosettig, *J. Amer. Chem. Soc.*, 1938, **60**, 1321). However, we could not prepare it by the reported procedure or by variations involving other conditions and other nitrosating agents, such as 2-ethoxyethyl nitrite, 2-*n*-butoxyethyl nitrite, and *N*-nitrosodimethylamine. Starting material was recovered when 2-acetylphenanthrene was treated with acetyl chloride and 2-ethoxyethyl nitrite (Claisen and Manasse, *Ber.*, 1887, **20**, 2194).

The objectionable physiological effects of the volatile alkyl nitrites were circumvented by the use of 2-*n*-butoxyethyl nitrite.

The high-melting impurity obtained by Bachmann (*J. Amer. Chem. Soc.*, 1935, **57**, 555) during the preparation of 1-benzoylphenanthrene was also encountered in the preparation and separation of 2- and 3-acetylphenanthrene. This material, shown to be anthraquinone by comparison with an authentic sample, was formed during the purification of phenanthrene by chromic acid oxidation of 90% phenanthrene.

Experimental.—M. p.s were determined with a calibrated apparatus. Microanalyses are by Galbraith Laboratories, Knoxville 17, Tennessee, U.S.A.

2-3′-*Phenanthrylquinoxaline*. A mixture of 3-acetylphenanthrene (44 g.) and selenium dioxide (87 g.) in ethanol (500 c.c.) was refluxed for 9 hr. and then filtered while hot; the filtrate, on cooling, deposited the impure glyoxal, which formed long silky needles, m. p. 82—83° (from ethanol), and was apparently a hydrated acetal (Found: C, 73·5; H, 5·7%). The *quinoxaline*, prepared by refluxing a solution of equivalent amounts of *o*-phenylenediamine and 3-phenanthrylglyoxal in ethanol for 5 min. and adding water, formed clusters of thin, pale-brown needles, m. p. 189—190° [from ethanol (charcoal)] (Found: C, 86·3; H, 4·6; N, 9·2. $C_{22}H_{14}N_2$ requires C, 86·3; H, 4·6; N, 9·1%).

3-*Phenanthrylglyoxal dithiosemicarbazone*. Prepared by refluxing a mixture of the crude glyoxal (7 g.) and thiosemicarbazide (13·6 g.) in ethanol (500 c.c.) for 20 min., the *dithiosemicarbazone* formed a brown-yellow powder, m. p. 242—244° (decomp.) (from ethyl acetate in a

Soxhlet extractor) (Found : C, 57·3; H, 4·1; N, 21·4. $C_{18}H_{16}N_6S_2$ requires C, 56·8; H, 4·2; N, 22·1%).

2-*Ethoxyethyl nitrite*. The nitrite was prepared from ethylene glycol monoethyl ether and nitrous acid according to Noyes's method (*Org. Synth.*, Coll. Vol. II, p. 108). The light-green *nitrite* distilled at 30—33°/15—20 mm. (Found : C, 39·7; H, 7·5; N, 11·0. $C_4H_9O_3N$ requires C, 40·3; H, 7·6; N, 11·8%).

2-n-*Butoxyethyl nitrite*. Prepared in the same manner, this *nitrite* (70%) was obtained as a yellow liquid, b. p. 65—66°/15—20 mm. (Found : C, 49·1; H, 8·9; N, 9·3. $C_6H_{13}O_3N$ requires C, 49·0; H, 8·9; N, 9·5%).

THE UNIVERSITY OF TENNESSEE, KNOXVILLE 16, TENNESSEE, U.S.A.
[Present Addresses : as in previous Note.]
[*Received, November 19th*, 1953.]

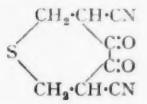
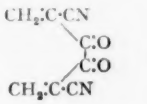
---

3 : 6-*Dicyanocatechol*.

By J. D. LOUDON and D. K. V. STEEL.

[Reprint Order No. 4875.]

A CRYSTALLINE, sulphur-free compound, produced by the interaction of bis-2-cyanoethyl sulphide and ethyl oxalate in presence of sodium ethoxide, proved to be 3 : 6-dicyanocatechol. Its structure was shown by (*a*) formation of a dimethyl ether and (*b*) hydrolysis and degradation to catechol *via* the 3 : 6- and 3-carboxylic acids. It is presumably formed from the thia*cyclo*heptane derivative (I) by elimination of hydrogen sulphide and cyclisation of the intermediate (II). Condensations of ethyl oxalate with bis-2-cyanoethylamine, with the corresponding *p*-toluenesulphonamide and with *NN*-bis-2-cyanoethylanisidine were attempted but only in the first case yielded a crystalline product, which is possibly 4-cyano-1-2′-cyanoethylpyrrolid-2 : 3-dione.

(I)  (II) 

Experimental.—3 : 6-*Dicyanocatechol*. Ethyl oxalate (5·2 g.) and then bis-2-cyanoethyl sulphide (5 g.) were added to an ethereal suspension of sodium ethoxide (from 1·64 g. of atomised sodium and 4·15 c.c. of ethanol). The whole was heated under reflux for 10 hr. and extracted with water. The acidified aqueous extract was exhausted by extraction with ether from which a semi-solid mass was recovered. Gummy material was removed by cautious washing with water, and the residual solid afforded 3 : 6-*dicyanocatechol* as needles, m. p. >330°, from water (Found : C, 60·2; H, 2·8; N, 17·5. $C_8H_4O_2N_2$ requires C, 60·0; H, 2·5; N, 17·5%). It gave a bright green colour with aqueous ferric chloride and in aqueous solution showed a faint blue fluorescence which changed to yellow-green on addition of alkali. Methylation with diazomethane afforded the *dimethyl ether* as needles, m. p. 109—110°, from light petroleum (b. p. 60—80°) (Found : C, 64·1; H, 4·2; N, 15·05. $C_{10}H_8O_2N_2$ requires C, 64·0; H, 4·3; N, 14·9%)

When 3 : 6-dicyanocatechol (0·1 g.) was heated under reflux with aqueous sodium hydroxide (50%; 4 g.) the initially formed yellow sodium salt dissolved, and acidification of the cooled solution gave 3 : 6-dicarboxycatechol, m. p. (decomp.) 290°, from water (Found : C, 44·4; H, 3·8. Calc. for $C_8H_6O_6,H_2O$: C, 44·45; H, 3·7%). This acid, which gave the characteristic blue-purple colour with aqueous ferric chloride, was partially decarboxylated when heated at 240—260° and finally at 300°, affording a sublimate of 3-carboxycatechol, m. p. (in sealed tube) 199—202°, from toluene. Decarboxylation was completed by heating 3-carboxycatechol for 1 hr. in aniline, catechol, (micro-) m. p. and mixed m. p. 98—100°, then being recovered in ether from a solution of the reaction mixture in aqueous acid.

(?)4-*Cyano*-1-2′-*cyanoethylpyrrolid*-2 : 3-*dione*. When bis-2-cyanoethylamine (4·4 g.) replaced the sulphide in the condensation with ethyl oxalate, a yellow sodium salt was formed after 1 hour's heating. This was collected, and its aqueous solution passed through ion-exchange

resin (IR-120H). Concentration of the emergent acidic solution *in vacuo* gave a gum which partly solidified. The solid formed creamy crystals, m. p. 175—177°, from water (Found: C, 49·6; H, 4·7; N, 21·5. $C_5H_7O_2N_3.H_2O$ requires C, 49·2; H, 4·65; N, 21·5%), which were acidic, but non-basic and gave a red colour with aqueous ferric chloride. Reaction with ethereal diazomethane afforded a *monomethyl ether*, m. p. 160—162°, from methanol (Found: C, 56·4; H, 4·7; N, 21·7. $C_9H_9O_2N_3$ requires C, 56·5; H, 4·75; N, 22·0%).

NN-*Bis*-2-*cyanoethyltoluene*-p-*sulphonamide*, m. p. 102° (from ethanol), was formed from bis-2-cyanoethylamine and toluene-*p*-sulphonyl chloride in cold pyridine (Found: C, 56·7; H, 5·0. $C_{13}H_{15}O_2N_3S$ requires C, 56·3; H, 5·45%).

UNIVERSITY OF GLASGOW.

[*Received, December 9th*, 1953.]

JOURNAL REPRINT SERVICE

THE CHEMICAL SOCIETY · BURLINGTON HOUSE · LONDON, W.1

Original papers published in the *Journal* of the Chemical Society, from January 1954, will be available from the Society in reprint form. Single reprints (without covers) may be obtained at 5*s*. ($0.75) each or books of vouchers can be purchased from the Society at 10*s*. ($1.50) per book or ten books for £4 10*s*. ($13.50). Each book contains five reprint vouchers that are valid for three years and can, during that time, be exchanged for reprints of any five scientific communications published in the *Journal*.

Every paper published in the *Journal* will carry a Reprint Order Number to be used in connection with this service, and the *Proceedings* (issued free each month with the *Journal*) will contain lists of papers accepted for publication. The papers so listed will normally appear in the *Journal* during the next succeeding two months, and if reprints are ordered promptly after the announcement of the title they will be distributed to subscribers at approximately the same time as the issue of the *Journal* in which the papers are published.

It is hoped that this service will enable specialists to obtain quickly reprints of those papers that are of interest to them in their particular branch of chemistry.

Reprints of Lectures published in the *Journal* are not available under the voucher system, but can be obtained price 5*s*. each.

A rough and shabby room

"For teaching chemistry, a laboratory is absolutely essential No matter how rough and shabby a room, so that it be well ventilated, have gas and water laid on, and will hold sixteen to twenty boys . . . the general laboratory stock, including a still, a stove or furnace, gas jars, a pneumatic trough, a proper set of retorts, crucibles, tubing, etc. and the necessary chemicals will cost under £12."

Standards, like prices, have gone up since 1869, when the first issue of Nature reproduced an address presented by the Rev. W. Tuckwell to the British Association Meeting in Exeter containing the above passage.

Much good work was done in the "rough and shabby rooms" of a century ago; but the layout and equipment of the modern laboratory, and the stocks of B.D.H. reagents on its shelves, bear witness to the standards that are considered essential to-day.

LABORATORY **B·D·H** CHEMICALS

THE BRITISH DRUG HOUSES LTD B.D.H. LABORATORY CHEMICALS GROUP POOLE DORSET

LCP/4F

PRINTED IN GREAT BRITAIN BY RICHARD CLAY AND COMPANY, LTD., BUNGAY, SUFFOLK.